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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PANCREATIC CANCER

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided on CD-ROM in lieu of a paper copy, and is hereby incorporated by reference into the specification. Three CD-ROMs are provided, containing identical copies of the sequence listing: CD-ROM No. 1 is labeled COPY 1, contains the file 566.app which is 2.9 MB and created on January 30, 2002; CD-ROM No.2 is labeled COPY 2, contains the file 566.app which is 2.9 MB and created on January 30, 2002; CD-ROM No. 3 is labeled CRF, contains the file 566.app which is 2.9 MB and created on January 30, 2002.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to therapy and diagnosis of cancer, such as pancreatic cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a pancreatic tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of pancreatic cancer.

Description of the Related Art.

Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention and/or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Current therapies for this common and difficult-to-treat disease include surgery and/or chemotherapy. Although 5-year survival rates after surgical removal of the pancreas and a large portion of the duodenum have improved, the procedure is only used on 9% of patients. Of these, the highest reported 5-year survival rate is in the range of 20%. Patients with advanced pancreatic cancer are treated primarily by chemotherapy. The objective of such therapy is to prolong patient survival. Surgery and irradiation are used as well to relieve pain and reduce organ blockage.

In spite of considerable research, pancreatic cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550;

(b) complements of the sequences provided in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550;

(d) sequences that hybridize to a sequence provided in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550, under moderately stringent conditions;

(e) sequences having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to a sequence of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550;

(f) sequences having at least 90% identity to a sequence of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550; and

(g) degenerate variants of a sequence provided in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of pancreatic tumor samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554, 4558-4560.

In certain preferred embodiments, the polypeptides and/or polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554, 4558-4560 or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

[redacted]

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, the pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or polynucleotide of the invention and an immunostimulant, such as an adjuvant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human

patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with pancreatic cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition as recited above. The patient may be afflicted with pancreatic cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or

CD8$^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a pancreatic cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample, e.g., tumor sample, serum sample, etc., obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a

predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS

SEQ ID NO:1 is the determined cDNA sequence of clone PANC1-R1, ID NO. 68811.

SEQ ID NO:2 is the determined cDNA sequence of clone PANC1-R2, ID NO. 68812.

SEQ ID NO:3 is the determined cDNA sequence of clone PANC1-R3, ID NO. 68813.

SEQ ID NO:4 is the determined cDNA sequence of clone PANC1-R4, ID NO. 68814.

SEQ ID NO:5 is the determined cDNA sequence of clone PANC1-R5, ID NO. 68815.

SEQ ID NO:6 is the determined cDNA sequence of clone PANC1-R6, ID NO. 68816.

SEQ ID NO:7 is the determined cDNA sequence of clone PANC1-R8, ID NO. 68818.

SEQ ID NO:8 is the determined cDNA sequence of clone PANC1-R10, ID NO. 68820.

SEQ ID NO:9 is the determined cDNA sequence of clone PANC1-R11, ID NO. 68821.

SEQ ID NO:10 is the determined cDNA sequence of clone PANC1-R12, ID NO. 68822.

SEQ ID NO:11 is the determined cDNA sequence of clone PANC1-R13, ID NO. 68823.

SEQ ID NO:12 is the determined cDNA sequence of clone PANC1-R14, ID NO. 68824.

SEQ ID NO:13 is the determined cDNA sequence of clone PANC1-R15, ID NO. 68825.

SEQ ID NO:14 is the determined cDNA sequence of clone PANC1-R16, ID NO. 68826.

SEQ ID NO:15 is the determined cDNA sequence of clone PANC1-R17, ID NO. 68827.

SEQ ID NO:16 is the determined cDNA sequence of clone PANC1-R18, ID NO. 68828.

SEQ ID NO:17 is the determined cDNA sequence of clone PANC1-R19, ID NO. 68829.

SEQ ID NO:18 is the determined cDNA sequence of clone PANC1-R20, ID NO. 68830.

SEQ ID NO:19 is the determined cDNA sequence of clone PANC1-R21, ID NO. 68917.

SEQ ID NO:20 is the determined cDNA sequence of clone PANC1-R22, ID NO. 68918.

SEQ ID NO:21 is the determined cDNA sequence of clone PANC1-R23, ID NO. 68919.

SEQ ID NO:22 is the determined cDNA sequence of clone PANC1-R24, ID NO. 68920.

SEQ ID NO:23 is the determined cDNA sequence of clone PANC1-R25, ID NO. 68921.

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SEQ ID NO:26 is the determined cDNA sequence of clone PANC1-R29, ID NO. 68925.

SEQ ID NO:27 is the determined cDNA sequence of clone PANC1-R30, ID NO. 68926.

SEQ ID NO:28 is the determined cDNA sequence of clone PANC1-R32, ID NO. 68928.

SEQ ID NO:29 is the determined cDNA sequence of clone PANC1-R33, ID NO. 68929.

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SEQ ID NO:32 is the determined cDNA sequence of clone PANC1-R37, ID NO. 68933.

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SEQ ID NO:34 is the determined cDNA sequence of clone PANC1-R40, ID NO. 68936.

SEQ ID NO:35 is the determined cDNA sequence of clone PANC1-R43, ID NO. 69117.

SEQ ID NO:36 is the determined cDNA sequence of clone PANC1-R44, ID NO. 69118.

SEQ ID NO:37 is the determined cDNA sequence of clone PANC1-R45, ID NO. 69119.

SEQ ID NO:38 is the determined cDNA sequence of clone PANC1-R46, ID NO. 69120.

SEQ ID NO:39 is the determined cDNA sequence of clone PANC1-R47, ID NO. 69126.

SEQ ID NO:40 is the determined cDNA sequence of clone PANC1-R50, ID NO. 69133.

SEQ ID NO:41 is the determined cDNA sequence of clone PANC1-R51, ID NO. 69134.

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SEQ ID NO:45 is the determined cDNA sequence of clone PANC1-R59, ID NO. 69142.

SEQ ID NO:46 is the determined cDNA sequence of clone PANC1-R64, ID NO. 69292.

SEQ ID NO:47 is the determined cDNA sequence of clone PANC1-R66, ID NO. 69294.

SEQ ID NO:48 is the determined cDNA sequence of clone PANC1-R67, ID NO. 69295.

SEQ ID NO:49 is the determined cDNA sequence of clone PANC1-R69, ID NO. 69297.

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SEQ ID NO:53 is the determined cDNA sequence of clone PANC1-R76 A, ID NO. 69304.

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SEQ ID NO:57 is the determined cDNA sequence of clone PANC1-R82, ID NO. 69310.

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SEQ ID NO:60 is the determined cDNA sequence of clone PANC1-R85, ID NO. 69313.

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SEQ ID NO:62 is the determined cDNA sequence of clone PANC1-R88, ID NO. 69316.

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SEQ ID NO:65 is the determined cDNA sequence of clone PANC1-R91, ID NO. 69319.

SEQ ID NO:66 is the determined cDNA sequence of clone PANC1-R94, ID NO. 69322.

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SEQ ID NO:69 is the predicted polypeptide sequence of clone PANC1-R64, ID NO. 69292.

SEQ ID NO:70 is the predicted polypeptide sequence of clone PANC1-R66, ID NO. 69294.

SEQ ID NO:71 is the predicted polypeptide sequence of clone PANC1-R76 A, ID NO. 69304.

SEQ ID NO:72 is the predicted polypeptide sequence of clone PANC1-R76 B, ID NO. 69304.

SEQ ID NO:73 is the predicted polypeptide sequence of clone PANC1-R85, ID NO. 69313.

SEQ ID NO:74 is the predicted polypeptide sequence of clone PANC1-R94, ID NO. 69322.

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SEQ ID NO:133 is the full-length determined cDNA sequence of clone RABGGTB

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SEQ ID NO:135 is the full-length determined cDNA sequence of clone FBL

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SEQ ID NO:137 is the full-length determined cDNA sequence of clone pM5

SEQ ID NO:138 is the full-length determined cDNA sequence of clone PSK-1

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SEQ ID NO:141 is the full-length determined cDNA sequence of clone GdX

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SEQ ID NO:145 is the full-length determined cDNA sequence of clone TFPI2

SEQ ID NO:146 is the full-length determined cDNA sequence of clone L6

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SEQ ID NO:151 is the full-length determined cDNA sequence of clone CTGF

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SEQ ID NO:162 is the full-length predicted amino acid sequence of clone CD24

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SEQ ID NO:236 is the determined cDNA sequence of clone 73385.1

SEQ ID NO:237 is the determined cDNA sequence of clone 73386.1

SEQ ID NO:238 is the determined cDNA sequence of clone 73387.1

SEQ ID NO:239 is the determined cDNA sequence of clone 73388.2

SEQ ID NO:240 is the determined cDNA sequence of clone 73388.3

SEQ ID NO:241 is the determined cDNA sequence of clone 73389.2

SEQ ID NO:242 is the determined cDNA sequence of clone 73389.3

SEQ ID NO:243 is the determined cDNA sequence of clone 73390.1

SEQ ID NO:244 is the determined cDNA sequence of clone 73391.2

SEQ ID NO:245 is the determined cDNA sequence of clone 73417.2

SEQ ID NO:246 is the determined cDNA sequence of clone 73392.1

SEQ ID NO:247 is the determined cDNA sequence of clone 73393.3

SEQ ID NO:248 is the determined cDNA sequence of clone 73418.1

SEQ ID NO:249 is the determined cDNA sequence of clone 73395.1

SEQ ID NO:250 is the determined cDNA sequence of clone 73396.1

SEQ ID NO:251 is the determined cDNA sequence of clone 73397.1

SEQ ID NO:252 is the determined cDNA sequence of clone 73419.3

SEQ ID NO:253 is the determined cDNA sequence of clone 73419.2

SEQ ID NO:254 is the determined cDNA sequence of clone 73398.1

SEQ ID NO:255 is the determined cDNA sequence of clone 73399.3

SEQ ID NO:256 is the determined cDNA sequence of clone 73399.2

SEQ ID NO:257 is the determined cDNA sequence of clone 73400.1

SEQ ID NO:258 is the determined cDNA sequence of clone 73420.3

SEQ ID NO:259 is the determined cDNA sequence of clone 73420.2

SEQ ID NO:260 is the determined cDNA sequence of clone 73401.1

SEQ ID NO:261 is the determined cDNA sequence of clone 73404.3

SEQ ID NO:262 is the determined cDNA sequence of clone 73405.1

SEQ ID NO:263 is the determined cDNA sequence of clone 73407.3

SEQ ID NO:264 is the determined cDNA sequence of clone 73407.2

SEQ ID NO:265 is the determined cDNA sequence of clone 72174.1

SEQ ID NO:266 is the determined cDNA sequence of clone 72175.1

SEQ ID NO:267 is the determined cDNA sequence of clone 72176.1

SEQ ID NO:268 is the determined cDNA sequence of clone 72177.1

SEQ ID NO:269 is the determined cDNA sequence of clone 72178.1

SEQ ID NO:270 is the determined cDNA sequence of clone 72179.1

SEQ ID NO:271 is the determined cDNA sequence of clone 73421.3

SEQ ID NO:272 is the determined cDNA sequence of clone 73421.2

SEQ ID NO:273 is the determined cDNA sequence of clone 72180.1

SEQ ID NO:274 is the determined cDNA sequence of clone 72181.1

SEQ ID NO:275 is the determined cDNA sequence of clone 72182.1

SEQ ID NO:276 is the determined cDNA sequence of clone 72183.1

SEQ ID NO:277 is the determined cDNA sequence of clone 72184.1

SEQ ID NO:278 is the determined cDNA sequence of clone 72185.1

SEQ ID NO:279 is the determined cDNA sequence of clone 72186.1

SEQ ID NO:280 is the determined cDNA sequence of clone 72187.1

SEQ ID NO:281 is the determined cDNA sequence of clone 72188.1

SEQ ID NO:282 is the determined cDNA sequence of clone 72189.1

SEQ ID NO:283 is the determined cDNA sequence of clone 72190.1

SEQ ID NO:284 is the determined cDNA sequence of clone 72191.1
SEQ ID NO:285 is the determined cDNA sequence of clone 72192.1
SEQ ID NO:286 is the determined cDNA sequence of clone 72193.1
SEQ ID NO:287 is the determined cDNA sequence of clone 72194.1
SEQ ID NO:288 is the determined cDNA sequence of clone 72195.1
SEQ ID NO:289 is the determined cDNA sequence of clone 72196.1
SEQ ID NO:290 is the determined cDNA sequence of clone 72197.1
SEQ ID NO:291 is the determined cDNA sequence of clone 72198.1
SEQ ID NO:292 is the determined cDNA sequence of clone 72199.1
SEQ ID NO:293 is the determined cDNA sequence of clone 72200.1
SEQ ID NO:294 is the determined cDNA sequence of clone 72201.1
SEQ ID NO:295 is the determined cDNA sequence of clone 72202.1
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SEQ ID NO:297 is the determined cDNA sequence of clone 72204.1
SEQ ID NO:298 is the determined cDNA sequence of clone 72205.1
SEQ ID NO:299 is the determined cDNA sequence of clone 72206.3
SEQ ID NO:300 is the determined cDNA sequence of clone 72206.2
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SEQ ID NO:302 is the determined cDNA sequence of clone 73423.1
SEQ ID NO:303 is the determined cDNA sequence of clone 73424.1
SEQ ID NO:304 is the determined cDNA sequence of clone 73425.3
SEQ ID NO:305 is the determined cDNA sequence of clone 73425.2
SEQ ID NO:306 is the determined cDNA sequence of clone 74597.2
SEQ ID NO:307 is the determined cDNA sequence of clone 73426.3
SEQ ID NO:308 is the determined cDNA sequence of clone 73426.2
SEQ ID NO:309 is the determined cDNA sequence of clone 73427.3
SEQ ID NO:310 is the determined cDNA sequence of clone 73427.2
SEQ ID NO:311 is the determined cDNA sequence of clone 73428.3
SEQ ID NO:312 is the determined cDNA sequence of clone 73429.3

SEQ ID NO:313 is the determined cDNA sequence of clone 74598.1
SEQ ID NO:314 is the determined cDNA sequence of clone 74598.2
SEQ ID NO:315 is the determined cDNA sequence of clone 74599.2
SEQ ID NO:316 is the determined cDNA sequence of clone 73430.3
SEQ ID NO:317 is the determined cDNA sequence of clone 74600.1
SEQ ID NO:318 is the determined cDNA sequence of clone 74600.2
SEQ ID NO:319 is the determined cDNA sequence of clone 74601.1
SEQ ID NO:320 is the determined cDNA sequence of clone 74602.2
SEQ ID NO:321 is the determined cDNA sequence of clone 73437.2
SEQ ID NO:322 is the determined cDNA sequence of clone 73437.3
SEQ ID NO:323 is the determined cDNA sequence of clone 73438.2
SEQ ID NO:324 is the determined cDNA sequence of clone 73438.3
SEQ ID NO:325 is the determined cDNA sequence of clone 73439.2
SEQ ID NO:326 is the determined cDNA sequence of clone 73439.3
SEQ ID NO:327 is the determined cDNA sequence of clone 73440.2
SEQ ID NO:328 is the determined cDNA sequence of clone 73440.3
SEQ ID NO:329 is the determined cDNA sequence of clone 73441.3
SEQ ID NO:330 is the determined cDNA sequence of clone 73442.2
SEQ ID NO:331 is the determined cDNA sequence of clone 73442.3
SEQ ID NO:332 is the determined cDNA sequence of clone 73443.2
SEQ ID NO:333 is the determined cDNA sequence of clone 73443.3
SEQ ID NO:334 is the determined cDNA sequence of clone 73444.2
SEQ ID NO:335 is the determined cDNA sequence of clone 73444.3
SEQ ID NO:336 is the determined cDNA sequence of clone 74602.1
SEQ ID NO:337 is the determined cDNA sequence of clone 73445.1
SEQ ID NO:338 is the determined cDNA sequence of clone 73456.1
SEQ ID NO:339 is the determined cDNA sequence of clone 73585.3
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SEQ ID NO:341 is the determined cDNA sequence of clone 73586.3

SEQ ID NO:342 is the determined cDNA sequence of clone 73587.2
SEQ ID NO:343 is the determined cDNA sequence of clone 73587.3
SEQ ID NO:344 is the determined cDNA sequence of clone 73457.2
SEQ ID NO:345 is the determined cDNA sequence of clone 73457.3
SEQ ID NO:346 is the determined cDNA sequence of clone 74603.1
SEQ ID NO:347 is the determined cDNA sequence of clone 74603.2
SEQ ID NO:348 is the determined cDNA sequence of clone 73458.1
SEQ ID NO:349 is the determined cDNA sequence of clone 73459.2
SEQ ID NO:350 is the determined cDNA sequence of clone 73459.3
SEQ ID NO:351 is the determined cDNA sequence of clone 73460.2
SEQ ID NO:352 is the determined cDNA sequence of clone 73460.3
SEQ ID NO:353 is the determined cDNA sequence of clone 73461.1
SEQ ID NO:354 is the determined cDNA sequence of clone 74604.1
SEQ ID NO:355 is the determined cDNA sequence of clone 74604.2
SEQ ID NO:356 is the determined cDNA sequence of clone 74605.1
SEQ ID NO:357 is the determined cDNA sequence of clone 74605.2
SEQ ID NO:358 is the determined cDNA sequence of clone 74606.1
SEQ ID NO:359 is the determined cDNA sequence of clone 74606.2
SEQ ID NO:360 is the determined cDNA sequence of clone 74607.1
SEQ ID NO:361 is the determined cDNA sequence of clone 74607.2
SEQ ID NO:362 is the determined cDNA sequence of clone 74608.1
SEQ ID NO:363 is the determined cDNA sequence of clone 74608.2
SEQ ID NO:364 is the determined cDNA sequence of clone 74610.2
SEQ ID NO:365 is the determined cDNA sequence of clone 74611.1
SEQ ID NO:366 is the determined cDNA sequence of clone 74613.1
SEQ ID NO:367 is the determined cDNA sequence of clone 74613.2
SEQ ID NO:368 is the determined cDNA sequence of clone 74614.1
SEQ ID NO:369 is the determined cDNA sequence of clone 74614.2
SEQ ID NO:370 is the determined cDNA sequence of clone 74640.2

SEQ ID NO:371 is the determined cDNA sequence of clone 74640.1

SEQ ID NO:372 is the determined cDNA sequence of clone 74615.2

SEQ ID NO:373 is the determined cDNA sequence of clone 74615.1

SEQ ID NO:374 is the determined cDNA sequence of clone 74616.2

SEQ ID NO:375 is the determined cDNA sequence of clone 74616.1

SEQ ID NO:376 is the determined cDNA sequence of clone 74617.2

SEQ ID NO:377 is the determined cDNA sequence of clone 77101.1

SEQ ID NO:378 is the determined cDNA sequence of clone 77102.1

SEQ ID NO:379 is the determined cDNA sequence of clone 77104.1

SEQ ID NO:380 is the determined cDNA sequence of clone 74618.1

SEQ ID NO:381 is the determined cDNA sequence of clone 74618.2

SEQ ID NO:382 is the determined cDNA sequence of clone 74619.2

SEQ ID NO:383 is the determined cDNA sequence of clone 74620.1

SEQ ID NO:384 is the determined cDNA sequence of clone 74620.2

SEQ ID NO:385 is the determined cDNA sequence of clone 74621.1

SEQ ID NO:386 is the determined cDNA sequence of clone 74621.2

SEQ ID NO:387 is the determined cDNA sequence of clone 74623.1

SEQ ID NO:388 is the determined cDNA sequence of clone 74623.2

SEQ ID NO:389 is the determined cDNA sequence of clone 74624.1

SEQ ID NO:390 is the determined cDNA sequence of clone 74624.2

SEQ ID NO:391 is the determined cDNA sequence of clone 74625.1

SEQ ID NO:392 is the determined cDNA sequence of clone 74625.2

SEQ ID NO:393 is the determined cDNA sequence of clone 74631.2

SEQ ID NO:394 is the determined cDNA sequence of clone 74632.1

SEQ ID NO:395 is the determined cDNA sequence of clone 74632.2

SEQ ID NO:396 is the determined cDNA sequence of clone 77105.1

SEQ ID NO:397 is the determined cDNA sequence of clone 77108.1

SEQ ID NO:398 is the determined cDNA sequence of clone 77109.1

SEQ ID NO:399 is the determined cDNA sequence of clone 77114.1

SEQ ID NO:400 is the determined cDNA sequence of clone 77118.1
SEQ ID NO:401 is the determined cDNA sequence of clone 77120.1
SEQ ID NO:402 is the determined cDNA sequence of clone 77122.1
SEQ ID NO:403 is the determined cDNA sequence of clone 77123.1
SEQ ID NO:404 is the determined cDNA sequence of clone 77125.1
SEQ ID NO:405 is the determined cDNA sequence of clone 77127.1
SEQ ID NO:406 is the determined cDNA sequence of clone 77129.1
SEQ ID NO:407 is the determined cDNA sequence of clone 77130.1
SEQ ID NO:408 is the determined cDNA sequence of clone 77132.1
SEQ ID NO:409 is the determined cDNA sequence of clone 77134.1
SEQ ID NO:410 is the determined cDNA sequence of clone 77135.1
SEQ ID NO:411 is the determined cDNA sequence of clone 77136.1
SEQ ID NO:412 is the determined cDNA sequence of clone 77139.1
SEQ ID NO:413 is the determined cDNA sequence of clone 77140.1
SEQ ID NO:414 is the determined cDNA sequence of clone 77141.1
SEQ ID NO:415 is the determined cDNA sequence of clone 77144.1
SEQ ID NO:416 is the determined cDNA sequence of clone 77146.1
SEQ ID NO:417 is the determined cDNA sequence of clone 77149.1
SEQ ID NO:418 is the determined cDNA sequence of clone 77474.1
SEQ ID NO:419 is the determined cDNA sequence of clone 77153.1
SEQ ID NO:420 is the determined cDNA sequence of clone 77479.1
SEQ ID NO:421 is the determined cDNA sequence of clone 77154.1
SEQ ID NO:422 is the determined cDNA sequence of clone 77155.1
SEQ ID NO:423 is the determined cDNA sequence of clone 77157.1
SEQ ID NO:424 is the determined cDNA sequence of clone 77480.1
SEQ ID NO:425 is the determined cDNA sequence of clone 77485.1
SEQ ID NO:426 is the determined cDNA sequence of clone 77487.1
SEQ ID NO:427 is the determined cDNA sequence of clone 77488.1
SEQ ID NO:428 is the determined cDNA sequence of clone 77490.1

SEQ ID NO:429 is the determined cDNA sequence of clone 77494.1

SEQ ID NO:430 is the determined cDNA sequence of clone 77495.1

SEQ ID NO:431 is the determined cDNA sequence of clone 77499.1

SEQ ID NO:432 is the determined cDNA sequence of clone 77500.1

SEQ ID NO:433 is the determined cDNA sequence of clone 77160.1

SEQ ID NO:434 is the determined cDNA sequence of clone 77504.1

SEQ ID NO:435 is the determined cDNA sequence of clone 77506.1

SEQ ID NO:436 is the determined cDNA sequence of clone 77507.1

SEQ ID NO:437 is the determined cDNA sequence of clone 77508.1

SEQ ID NO:438 is the determined cDNA sequence of clone 77509.1

SEQ ID NO:439 is the determined cDNA sequence of clone 77162.1

SEQ ID NO:440 is the determined cDNA sequence of clone 77163.1

SEQ ID NO:441 is the determined cDNA sequence of clone 77165.1

SEQ ID NO:442 is the determined cDNA sequence of clone 77167.1

SEQ ID NO:443 is the determined cDNA sequence of clone 77169.1

SEQ ID NO:444 is the determined cDNA sequence of clone 77171.1

SEQ ID NO:445 is the determined cDNA sequence of clone 77172.1

SEQ ID NO:446 is the determined cDNA sequence of clone 77173.1

SEQ ID NO:447 is the determined cDNA sequence of clone 77175.1

SEQ ID NO:448 is the determined cDNA sequence of clone 77176.1

SEQ ID NO:449 is the determined cDNA sequence of clone 77178.1

SEQ ID NO:450 is the determined cDNA sequence of clone 77180.1

SEQ ID NO:451 is the determined cDNA sequence of clone 77510.1

SEQ ID NO:452 is the full-length determined cDNA sequence for coxIII

SEQ ID NO:453 is the full-length predicted amino acid sequence of coxIII

SEQ ID NO:454 is the determined full-length cDNA sequence of clone 80186 (also referred to as Pn80E), extending the sequence set forth in SEQ ID NO:105

SEQ ID NO:455 is the full-length cDNA sequence of Pn81E.

SEQ ID NO:456 is the determined cDNA sequence of clone PaSLBH2c1

SEQ ID NO:457 is the determined cDNA sequence of clone PaSLBH2c2
SEQ ID NO:458 is the determined cDNA sequence of clone PaSLBH2c3
SEQ ID NO:459 is the determined cDNA sequence of clone PaSLBH2c4
SEQ ID NO:460 is the determined cDNA sequence of clone PaSLBH2c5
SEQ ID NO:461 is the determined cDNA sequence of clone PaSLBH2c7
SEQ ID NO:462 is the determined cDNA sequence of clone PaSLBH2c8
SEQ ID NO:463 is the determined cDNA sequence of clone PaSLBH2c9
SEQ ID NO:464 is the determined cDNA sequence of clone PaSLBH2c10
SEQ ID NO:465 is the determined cDNA sequence of clone PaSLBH2c11
SEQ ID NO:466 is the determined cDNA sequence of clone PaSLBH2c12
SEQ ID NO:467 is the determined cDNA sequence of clone PaSLBH2c13
SEQ ID NO:468 is the determined cDNA sequence of clone PaSLBH2c14
SEQ ID NO:469 is the determined cDNA sequence of clone PaSLBH2c15
SEQ ID NO:470 is the determined cDNA sequence of clone PaSLBH2c16
SEQ ID NO:471 is the determined cDNA sequence of clone PaSLBH2c17
SEQ ID NO:472 is the determined cDNA sequence of clone PaSLBH2c18
SEQ ID NO:473 is the determined cDNA sequence of clone PaSLBH2c19
SEQ ID NO:474 is the determined cDNA sequence of clone PaSLBH2c20
SEQ ID NO:475 is the determined cDNA sequence of clone PaSLBH2c21
SEQ ID NO:476 is the determined cDNA sequence of clone PaSLBH2c22
SEQ ID NO:477 is the determined cDNA sequence of clone PaSLBH2c23
SEQ ID NO:478 is the determined cDNA sequence of clone PaSLBH2c24
SEQ ID NO:479 is the determined cDNA sequence of clone PaSLBH2c25
SEQ ID NO:480 is the determined cDNA sequence of clone PaSLBH2c26
SEQ ID NO:481 is the determined cDNA sequence of clone PaSLBH2c27
SEQ ID NO:482 is the determined cDNA sequence of clone PaSLBH2c28
SEQ ID NO:483 is the determined cDNA sequence of clone PaSLBH2c29
SEQ ID NO:484 is the determined cDNA sequence of clone PaSLBH2c30
SEQ ID NO:485 is the determined cDNA sequence of clone PaSLBH2c31

SEQ ID NO:486 is the determined cDNA sequence of clone PaSLBH2c32

SEQ ID NO:487 is the determined cDNA sequence of clone PaSLBH2c33

SEQ ID NO:488 is the determined cDNA sequence of clone PaSLBH2c34

SEQ ID NO:489 is the determined cDNA sequence of clone PaSLBH2c35

SEQ ID NO:490 is the determined cDNA sequence of clone PaSLBH2c36

SEQ ID NO:491 is the determined cDNA sequence of clone PaSLBH2c37

SEQ ID NO:492 is the determined cDNA sequence of clone PaSLBH2c38

SEQ ID NO:493 is the determined cDNA sequence of clone PaSLBH2c39

SEQ ID NO:494 is the determined cDNA sequence of clone PASLBH2bc1

SEQ ID NO:495 is the determined cDNA sequence of clone PASLBH2bc2

SEQ ID NO:496 is the determined cDNA sequence of clone PASLBH2bc3

SEQ ID NO:497 is the determined cDNA sequence of clone PASLBH2bc4

SEQ ID NO:498 is the determined cDNA sequence of clone PASLBH2bc5

SEQ ID NO:499 is the determined cDNA sequence of clone PASLBH2bc6

SEQ ID NO:500 is the determined cDNA sequence of clone PASLBH2bc7

SEQ ID NO:501 is the determined cDNA sequence of clone PASLBH2bc8

SEQ ID NO:502 is the determined cDNA sequence of clone PASLBH2bc10

SEQ ID NO:503 is the determined cDNA sequence of clone PASLBH2bc11

SEQ ID NO:504 is the determined cDNA sequence of clone PASLBH2bc12

SEQ ID NO:505 is the determined cDNA sequence of clone PASLBH2bc13

SEQ ID NO:506 is the determined cDNA sequence of clone PASLBH2bc14

SEQ ID NO:507 is the determined cDNA sequence of clone PASLBH2bc15

SEQ ID NO:508 is the determined cDNA sequence of clone PASLBH2bc16

SEQ ID NO:509 is the determined cDNA sequence of clone PASLBH2bc17

SEQ ID NO:510 is the determined cDNA sequence of clone PASLBH2bc18

SEQ ID NO:511 is the determined cDNA sequence of clone PASLBH2bc19

SEQ ID NO:512 is the determined cDNA sequence of clone PASLBH2bc20

SEQ ID NO:513 is the determined cDNA sequence of clone PASLBH2bc21

SEQ ID NO:514 is the determined cDNA sequence of clone PASLBH2bc22

SEQ ID NO:515 is the determined cDNA sequence of clone PASLBH2bc23
SEQ ID NO:516 is the determined cDNA sequence of clone PASLBH2bc24
SEQ ID NO:517 is the determined cDNA sequence of clone PASLBH2bc25
SEQ ID NO:518 is the determined cDNA sequence of clone PASLBH2bc26
SEQ ID NO:519 is the determined cDNA sequence of clone PASLBH2bc27
SEQ ID NO:520 is the determined cDNA sequence of clone PASLBH2bc28
SEQ ID NO:521 is the determined cDNA sequence of clone PASLBH2bc29
SEQ ID NO:522 is the determined cDNA sequence of clone PASLBH2bc30
SEQ ID NO:523 is the determined cDNA sequence of clone PASLBH2bc31
SEQ ID NO:524 is the determined cDNA sequence of clone PASLBH2bc32
SEQ ID NO:525 is the determined cDNA sequence of clone PASLBH2bc33
SEQ ID NO:526 is the determined cDNA sequence of clone PASLBH2bc35
SEQ ID NO:527 is the determined cDNA sequence of clone PASLBH2bc36
SEQ ID NO:528 is the determined cDNA sequence of clone PASLBH2bc37
SEQ ID NO:529 is the determined cDNA sequence of clone 61219685
SEQ ID NO:530 is the determined cDNA sequence of clone 61219686
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SEQ ID NO:534 is the determined cDNA sequence of clone 61219691
SEQ ID NO:535 is the determined cDNA sequence of clone 61219692
SEQ ID NO:536 is the determined cDNA sequence of clone 61219693
SEQ ID NO:537 is the determined cDNA sequence of clone 61219694
SEQ ID NO:538 is the determined cDNA sequence of clone 61219695
SEQ ID NO:539 is the determined cDNA sequence of clone 61219696
SEQ ID NO:540 is the determined cDNA sequence of clone 61219697
SEQ ID NO:541 is the determined cDNA sequence of clone 61219698
SEQ ID NO:542 is the determined cDNA sequence of clone 61219699
SEQ ID NO:543 is the determined cDNA sequence of clone 61219700

SEQ ID NO:544 is the determined cDNA sequence of clone 61219701
SEQ ID NO:545 is the determined cDNA sequence of clone 61219704
SEQ ID NO:546 is the determined cDNA sequence of clone 61219705
SEQ ID NO:547 is the determined cDNA sequence of clone 61219706
SEQ ID NO:548 is the determined cDNA sequence of clone 61219708
SEQ ID NO:549 is the determined cDNA sequence of clone 61219709
SEQ ID NO:550 is the determined cDNA sequence of clone 61219710
SEQ ID NO:551 is the determined cDNA sequence of clone 61219711
SEQ ID NO:552 is the determined cDNA sequence of clone 61219712
SEQ ID NO:553 is the determined cDNA sequence of clone 61219713
SEQ ID NO:554 is the determined cDNA sequence of clone 61219714
SEQ ID NO:555 is the determined cDNA sequence of clone 61219715
SEQ ID NO:556 is the determined cDNA sequence of clone 61219716
SEQ ID NO:557 is the determined cDNA sequence of clone 61219717
SEQ ID NO:558 is the determined cDNA sequence of clone 61219718
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SEQ ID NO:560 is the determined cDNA sequence of clone 61219721
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SEQ ID NO:564 is the determined cDNA sequence of clone 61219727
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SEQ ID NO:573 is the determined cDNA sequence of clone 61219738

SEQ ID NO:574 is the determined cDNA sequence of clone 61219739

SEQ ID NO:575 is the determined cDNA sequence of clone 61219740

SEQ ID NO:576 is the determined cDNA sequence of clone 61219741

SEQ ID NO:577 is the determined cDNA sequence of clone 61219742

SEQ ID NO:578 is the determined cDNA sequence of clone 61219744

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SEQ ID NO:580 is the determined cDNA sequence of clone 61219747

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SEQ ID NO:583 is the determined cDNA sequence of clone 61219750

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SEQ ID NO:585 is the determined cDNA sequence of clone 61219753

SEQ ID NO:586 is the determined cDNA sequence of clone 61219755

SEQ ID NO:587 is the determined cDNA sequence of clone 61219756

SEQ ID NO:588 is the determined cDNA sequence of clone 61219757

SEQ ID NO:589 is the determined cDNA sequence of clone 61219759

SEQ ID NO:590 is the determined cDNA sequence of clone 61219761

SEQ ID NO:591 is the determined cDNA sequence of clone 61219762

SEQ ID NO:592 is the determined cDNA sequence of clone 61219763

SEQ ID NO:593 is the determined cDNA sequence of clone 61219764

SEQ ID NO:594 is the determined cDNA sequence of clone 61219765

SEQ ID NO:595 is the determined cDNA sequence of clone 61219766

SEQ ID NO:596 is the determined cDNA sequence of clone 61219767

SEQ ID NO:597 is the determined cDNA sequence of clone 61219768

SEQ ID NO:598 is the determined cDNA sequence of clone 61219771

SEQ ID NO:599 is the determined cDNA sequence of clone 61219772

SEQ ID NO:600 is the determined cDNA sequence of clone 61219773

SEQ ID NO:601 is the determined cDNA sequence of clone 61219774

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SEQ ID NO:632 is the determined cDNA sequence of clone 61220089

SEQ ID NO:633 is the determined cDNA sequence of clone 61220090

SEQ ID NO:634 is the determined cDNA sequence of clone 61220091

SEQ ID NO:635 is the determined cDNA sequence of clone 61220093

SEQ ID NO:636 is the determined cDNA sequence of clone 61220094

SEQ ID NO:637 is the determined cDNA sequence of clone 61220095

SEQ ID NO:638 is the determined cDNA sequence of clone 61220096

SEQ ID NO:639 is the determined cDNA sequence of clone 61220097

SEQ ID NO:640 is the determined cDNA sequence of clone 61220099

SEQ ID NO:641 is the determined cDNA sequence of clone 61220100

SEQ ID NO:642 is the determined cDNA sequence of clone 61220101

SEQ ID NO:643 is the determined cDNA sequence of clone 61220104

SEQ ID NO:644 is the determined cDNA sequence of clone 61220105

SEQ ID NO:645 is the determined cDNA sequence of clone 61220106

SEQ ID NO:646 is the determined cDNA sequence of clone 61220107

SEQ ID NO:647 is the determined cDNA sequence of clone 61220108

SEQ ID NO:648 is the determined cDNA sequence of clone 61220109

SEQ ID NO:649 is the determined cDNA sequence of clone 61220110

SEQ ID NO:650 is the determined cDNA sequence of clone 61220112

SEQ ID NO:651 is the determined cDNA sequence of clone 61220113

SEQ ID NO:652 is the determined cDNA sequence of clone 61220114

SEQ ID NO:653 is the determined cDNA sequence of clone 61220115

SEQ ID NO:654 is the determined cDNA sequence of clone 61220116

SEQ ID NO:655 is the determined cDNA sequence of clone 61220117

SEQ ID NO:656 is the determined cDNA sequence of clone 61220118

SEQ ID NO:657 is the determined cDNA sequence of clone 61220119

SEQ ID NO:658 is the determined cDNA sequence of clone 61220120

SEQ ID NO:659 is the determined cDNA sequence of clone 61220121

SEQ ID NO:660 is the determined cDNA sequence of clone 61220122
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SEQ ID NO:667 is the determined cDNA sequence of clone 61220130
SEQ ID NO:668 is the determined cDNA sequence of clone 61220133
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SEQ ID NO:670 is the determined cDNA sequence of clone 61220135
SEQ ID NO:671 is the determined cDNA sequence of clone 61220137
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SEQ ID NO:676 is the determined cDNA sequence of clone 61220143
SEQ ID NO:677 is the determined cDNA sequence of clone 61220144
SEQ ID NO:678 is the determined cDNA sequence of clone 61220146
SEQ ID NO:679 is the determined cDNA sequence of clone 61220147
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SEQ ID NO:4347 is the determined cDNA sequence of clone p0150r07c17
SEQ ID NO:4348 is the determined cDNA sequence of clone p0150r09c15
SEQ ID NO:4349 is the determined cDNA sequence of clone p0150r07c14
SEQ ID NO:4350 is the determined cDNA sequence of clone p0150r11c05
SEQ ID NO:4351 is the determined cDNA sequence of clone p0160r06c18
SEQ ID NO:4352 is the determined cDNA sequence of clone p0160r02c21
SEQ ID NO:4353 is the determined cDNA sequence of clone p0160r13c02
SEQ ID NO:4354 is the determined cDNA sequence of clone p0150r13c04
SEQ ID NO:4355 is the determined cDNA sequence of clone p0150r02c15
SEQ ID NO:4356 is the determined cDNA sequence of clone p0150r06c12
SEQ ID NO:4357 is the determined cDNA sequence of clone p0151r06c12
SEQ ID NO:4358 is the determined cDNA sequence of clone p0150r14c04
SEQ ID NO:4359 is the determined cDNA sequence of clone p0150r02c06
SEQ ID NO:4360 is the determined cDNA sequence of clone p0150r04c19
SEQ ID NO:4361 is the determined cDNA sequence of clone p0150r03c18
SEQ ID NO:4362 is the determined cDNA sequence of clone p0151r13c03
SEQ ID NO:4363 is the determined cDNA sequence of clone p0150r01c08
SEQ ID NO:4364 is the determined cDNA sequence of clone p0150r11c07
SEQ ID NO:4365 is the determined cDNA sequence of clone p0150r02c11
SEQ ID NO:4366 is the determined cDNA sequence of clone p0150r01c17
SEQ ID NO:4367 is the determined cDNA sequence of clone p0150r05c16
SEQ ID NO:4368 is the determined cDNA sequence of clone p0150r06c04
SEQ ID NO:4369 is the determined cDNA sequence of clone p0150r15c17
SEQ ID NO:4370 is the determined cDNA sequence of clone p0150r15c11
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SEQ ID NO:4372 is the determined cDNA sequence of clone p0150r13c03

SEQ ID NO:4373 is the determined cDNA sequence of clone p0150r09c10

SEQ ID NO:4374 is the determined cDNA sequence of clone p0161r13c17

SEQ ID NO:4375 is the determined cDNA sequence of clone p0159r16c21

SEQ ID NO:4376 is the determined cDNA sequence of clone p0150r02c02

SEQ ID NO:4377 is the determined cDNA sequence of clone p0151r09c19

SEQ ID NO:4378 is the determined cDNA sequence of clone p0151r02c06

SEQ ID NO:4379 is the determined cDNA sequence of clone p0150r16c06

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SEQ ID NO:4381 is the determined cDNA sequence of clone p0150r07c06

SEQ ID NO:4382 is the determined cDNA sequence of clone p0150r06c19

SEQ ID NO:4383 is the determined cDNA sequence of clone p0150r04c05

SEQ ID NO:4384 is the determined cDNA sequence of clone p0150r03c21

SEQ ID NO:4385 is the determined cDNA sequence of clone p0150r02c18

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SEQ ID NO:4387 is the determined cDNA sequence of clone p0150r10c15

SEQ ID NO:4388 is the determined cDNA sequence of clone p0150r07c05

SEQ ID NO:4389 is the determined cDNA sequence of clone p0150r06c08

SEQ ID NO:4390 is the determined cDNA sequence of clone p0150r01c24

SEQ ID NO:4391 is the determined cDNA sequence of clone p0150r07c15

SEQ ID NO:4392 is the determined cDNA sequence of clone p0150r02c23

SEQ ID NO:4393 is the determined cDNA sequence of clone p0151r09c08

SEQ ID NO:4394 is the determined cDNA sequence of clone p0150r16c09

SEQ ID NO:4395 is the determined cDNA sequence of clone p0150r14c11

SEQ ID NO:4396 is the determined cDNA sequence of clone p0151r05c12

SEQ ID NO:4397 is the determined cDNA sequence of clone p0150r12c23

SEQ ID NO:4398 is the determined cDNA sequence of clone p0150r16c02

SEQ ID NO:4399 is the determined cDNA sequence of clone p0155r10c08

SEQ ID NO:4400 is the determined cDNA sequence of clone p0150r02c05

SEQ ID NO:4401 is the determined cDNA sequence of clone p0150r09c04

SEQ ID NO:4402 is the determined cDNA sequence of clone p0150r03c22

SEQ ID NO:4403 is the determined cDNA sequence of clone p0150r15c10

SEQ ID NO:4404 is the determined cDNA sequence of clone p0150r13c20

SEQ ID NO:4405 is the determined cDNA sequence of clone p0150r08c18

SEQ ID NO:4406 is the determined cDNA sequence of clone p0150r09c22

SEQ ID NO:4407 is the determined cDNA sequence of clone p0157r08c09

SEQ ID NO:4408 is the determined cDNA sequence of clone p0163r04c09

SEQ ID NO:4409 is the determined cDNA sequence of clone p0155r01c04

SEQ ID NO:4410 is the determined cDNA sequence of clone p0152r16c22

SEQ ID NO:4411 is the determined cDNA sequence of clone p0152r16c12

SEQ ID NO:4412 is the determined cDNA sequence of clone p0150r01c16

SEQ ID NO:4413 is the determined cDNA sequence of clone p0150r05c23

SEQ ID NO:4414 is the determined cDNA sequence of clone p0150r11c09

SEQ ID NO:4415 is the determined cDNA sequence of clone p0150r13c22

SEQ ID NO:4416 is the determined cDNA sequence of clone p0150r11c17

SEQ ID NO:4417 is the determined cDNA sequence of clone p0159r16c01

SEQ ID NO:4418 is the determined cDNA sequence of clone p0156r16c21

SEQ ID NO:4419 is the determined cDNA sequence of clone p0150r06c15

SEQ ID NO:4420 is the determined cDNA sequence of clone p0151r05c04

SEQ ID NO:4421 is the determined cDNA sequence of clone p0150r05c21

SEQ ID NO:4422 is the determined cDNA sequence of clone p0150r11c22

SEQ ID NO:4423 is the determined cDNA sequence of clone p0150r01c14

SEQ ID NO:4424 is the determined cDNA sequence of clone p0150r15c08

SEQ ID NO:4425 is the determined cDNA sequence of clone p0150r11c02

SEQ ID NO:4426 is the determined cDNA sequence of clone p0157r07c21

SEQ ID NO:4427 is the determined cDNA sequence of clone p0150r16c17

SEQ ID NO:4428 is the determined cDNA sequence of clone p0155r03c08

SEQ ID NO:4429 is the determined cDNA sequence of clone p0150r07c10

SEQ ID NO:4430 is the determined cDNA sequence of clone p0150r16c13

SEQ ID NO:4431 is the determined cDNA sequence of clone p0150r06c10

SEQ ID NO:4432 is the determined cDNA sequence of clone p0150r02c16

SEQ ID NO:4433 is the determined cDNA sequence of clone p0150r09c06

SEQ ID NO:4434 is the determined cDNA sequence of clone p0150r11c16

SEQ ID NO:4435 is the determined cDNA sequence of clone p0150r01c13

SEQ ID NO:4436 is the determined cDNA sequence of clone p0150r08c10

SEQ ID NO:4437 is the determined cDNA sequence of clone p0150r05c18

SEQ ID NO:4438 is the determined cDNA sequence of clone p0159r14c18

SEQ ID NO:4439 is the determined cDNA sequence of clone p0150r16c22

SEQ ID NO:4440 is the determined cDNA sequence of clone p0152r10c20

SEQ ID NO:4441 is the determined cDNA sequence of clone p0150r13c23

SEQ ID NO:4442 is the determined cDNA sequence of clone p0150r12c10

SEQ ID NO:4443 is the determined cDNA sequence of clone p0150r09c18

SEQ ID NO:4444 is the determined cDNA sequence of clone p0158r09c04

SEQ ID NO:4445 is the determined cDNA sequence of clone p0150r08c09

SEQ ID NO:4446 is the determined cDNA sequence of clone p0150r11c11

SEQ ID NO:4447 is the determined cDNA sequence of clone p0150r15c01

SEQ ID NO:4448 is the determined cDNA sequence of clone p0157r07c01

SEQ ID NO:4449 is the determined cDNA sequence of clone p0150r09c21

SEQ ID NO:4450 is the determined cDNA sequence of clone p0150r12c02

SEQ ID NO:4451 is the determined cDNA sequence of clone p0150r03c17

SEQ ID NO:4452 is the determined cDNA sequence of clone p0157r07c20

SEQ ID NO:4453 is the determined cDNA sequence of clone p0150r05c20

SEQ ID NO:4454 is the determined cDNA sequence of clone p0150r05c04

SEQ ID NO:4455 is the determined cDNA sequence of clone p0150r07c12

SEQ ID NO:4456 is the determined cDNA sequence of clone p0150r05c02

SEQ ID NO:4457 is the determined cDNA sequence of clone p0152r13c24

SEQ ID NO:4458 is the determined cDNA sequence of clone p0150r03c11

SEQ ID NO:4459 is the determined cDNA sequence of clone p0162r13c11
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SEQ ID NO:4462 is the determined cDNA sequence of clone p0151r08c17
SEQ ID NO:4463 is the determined cDNA sequence of clone p0150r01c02
SEQ ID NO:4464 is the determined cDNA sequence of clone p0150r04c06
SEQ ID NO:4465 is the determined cDNA sequence of clone p0150r09c19
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SEQ ID NO:4467 is the determined cDNA sequence of clone p0150r02c20
SEQ ID NO:4468 is the determined cDNA sequence of clone p0155r09c08
SEQ ID NO:4469 is the determined cDNA sequence of clone p0152r16c01
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SEQ ID NO:4473 is the determined cDNA sequence of clone p0155r10c24
SEQ ID NO:4474 is the determined cDNA sequence of clone p0157r06c03
SEQ ID NO:4475 is the determined cDNA sequence of clone p0150r05c24
SEQ ID NO:4476 is the determined cDNA sequence of clone p0150r11c04
SEQ ID NO:4477 is the determined cDNA sequence of clone p0156r16c18
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SEQ ID NO:4485 is the determined cDNA sequence of clone p0157r05c21
SEQ ID NO:4486 is the determined cDNA sequence of clone p0157r06c05
SEQ ID NO:4487 is the determined cDNA sequence of clone p0157r06c05

SEQ ID NO:4488 is the determined cDNA sequence of clone p0150r15c22
SEQ ID NO:4489 is the determined cDNA sequence of clone p0159r03c13
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SEQ ID NO:4493 is the determined cDNA sequence of clone p0150r13c24
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SEQ ID NO:4495 is the determined cDNA sequence of clone p0150r05c19
SEQ ID NO:4496 is the determined cDNA sequence of clone p0150r07c01
SEQ ID NO:4497 is the determined cDNA sequence of clone p0150r06c16
SEQ ID NO:4498 is the determined cDNA sequence of clone p0150r02c07
SEQ ID NO:4499 is the determined cDNA sequence of clone p0152r15c23
SEQ ID NO:4500 is the determined cDNA sequence of clone p0150r11c01
SEQ ID NO:4501 is the determined cDNA sequence of clone p0150r03c14
SEQ ID NO:4502 is the determined cDNA sequence of clone p0150r02c12
SEQ ID NO:4503 is the determined cDNA sequence of clone p0150r04c17
SEQ ID NO:4504 is the determined cDNA sequence of clone p0150r01c04
SEQ ID NO:4505 is the determined cDNA sequence of clone p0150r02c22
SEQ ID NO:4506 is the determined cDNA sequence of clone p0150r09c01
SEQ ID NO:4507 is the determined cDNA sequence of clone p0150r08c17
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SEQ ID NO:4509 is the determined cDNA sequence of clone p0150r09c20
SEQ ID NO:4510 is the determined cDNA sequence of clone p0150r08c06
SEQ ID NO:4511 is the determined cDNA sequence of clone p0150r13c19
SEQ ID NO:4512 is the determined cDNA sequence of clone p0150r12c09
SEQ ID NO:4513 is the determined cDNA sequence of clone p0150r11c03
SEQ ID NO:4514 is the determined cDNA sequence of clone p0150r12c08
SEQ ID NO:4515 is the determined cDNA sequence of clone p0150r05c22
SEQ ID NO:4516 is the determined cDNA sequence of clone p0150r09c11

SEQ ID NO:4517 is the determined cDNA sequence of clone p0150r15c23
SEQ ID NO:4518 is the determined cDNA sequence of clone p0157r05c17
SEQ ID NO:4519 is the determined cDNA sequence of clone p0157r07c13
SEQ ID NO:4520 is the determined cDNA sequence of clone p0157r07c14
SEQ ID NO:4521 is the determined cDNA sequence of clone p0157r07c15
SEQ ID NO:4522 is the determined cDNA sequence of clone p0151r01c08
SEQ ID NO:4523 is the determined cDNA sequence of clone p0155r07c16
SEQ ID NO:4524 is the determined cDNA sequence of clone p0152r06c10
SEQ ID NO:4525 is the determined cDNA sequence of clone p0150r04c18
SEQ ID NO:4526 is the determined cDNA sequence of clone p0150r02c03
SEQ ID NO:4527 is the determined cDNA sequence of clone p0150r06c24
SEQ ID NO:4528 is the determined cDNA sequence of clone p0150r11c14
SEQ ID NO:4529 is the determined cDNA sequence of clone p0157r05c18
SEQ ID NO:4530 is the determined cDNA sequence of clone p0157r06c17
SEQ ID NO:4531 is the determined cDNA sequence of clone p0157r07c18
SEQ ID NO:4532 is the determined cDNA sequence of clone p0157r06c08
SEQ ID NO:4533 is the determined cDNA sequence of clone p0157r07c23
SEQ ID NO:4534 is the determined cDNA sequence of clone p0150r01c20
SEQ ID NO:4535 is the determined cDNA sequence of clone p0150r14c15
SEQ ID NO:4536 is the determined cDNA sequence of clone p0150r15c06
SEQ ID NO:4537 is the determined cDNA sequence of clone p0151r12c17
SEQ ID NO:4538 is the determined cDNA sequence of clone p0155r12c15
SEQ ID NO:4539 is the determined cDNA sequence of clone p0157r07c09
SEQ ID NO:4540 is the determined cDNA sequence of clone p0157r08c05
SEQ ID NO:4541 is the determined cDNA sequence of clone p0157r08c17
SEQ ID NO:4542 is the determined cDNA sequence of clone p0160r03c01
SEQ ID NO:4543 is the determined cDNA sequence of clone p0161r16c06
SEQ ID NO:4544 is the determined cDNA sequence of clone p0162r02c05
SEQ ID NO:4545 is the determined cDNA sequence of clone p0157r06c24

SEQ ID NO:4546 is the determined cDNA sequence of clone p0157r07c06

SEQ ID NO:4547 is the determined full length cDNA sequence of Pn1467P

SEQ ID NO:4548 is the determined full length cDNA sequence of Pn1468P

SEQ ID NO:4549 is the determined full length cDNA sequence of Pn1472P

SEQ ID NO:4550 is the determined full length cDNA sequence of Pn1475P

SEQ ID NO:4551 is the full length protein sequence of Pn1467P

SEQ ID NO:4552 is the full length protein sequence of Pn1468P

SEQ ID NO:4553 is the full length protein sequence of Pn1472P

SEQ ID NO:4554 is the full length protein sequence of Pn1475P

SEQ ID NO:4555 is the full length cDNA sequence of Pn1509P.

SEQ ID NO:4556 is the full length cDNA sequence of Pn1510P-short, encoding a 243 amino acid ORF of Pn1510P as set forth in SEQ ID NO:4559.

SEQ ID NO:4557 is the full length cDNA sequence of Pn1510P-long, encoding a 278 amino acid ORF of Pn1510P as set forth in SEQ ID NO:4560.

SEQ ID NO:4558 is the full length protein sequence of Pn1509P, encoded by the cDNA set forth in SEQ ID NO:4555.

SEQ ID NO:4559 is the amino acid sequence of the Pn1510P-243 ORF encoded by the cDNA sequence set forth in SEQ ID NO:4556.

SEQ ID NO:4560 is the amino acid sequence of the Pn1510P-278 ORF encoded by the cDNA sequence set forth in SEQ ID NO:4557.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly pancreatic cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.*, T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i*.e., antigenic determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550. Certain other illustrative polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554 and 4558-4560.

The polypeptides of the present invention are sometimes herein referred to as pancreatic tumor proteins or pancreatic tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in pancreatic tumor samples. Thus, a "pancreatic tumor polypeptide" or "pancreatic tumor protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of pancreatic tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of pancreatic tumor samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal tissues, as determined using a representative assay provided herein. A pancreatic tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with pancreatic cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera

to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.,* specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.,* they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (*e.g.,* in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other illustrative immunogenic portions will contain a small N- and/or C-terminal deletion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide compositions set forth herein, such as those set forth in SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554 and 4558-4560, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about

50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can

be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes,

substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparaginc; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other

sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* *5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* *4*:11-17; Robinson, E.D. (1971) *Comb. Theor* *11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* *4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* *80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl.*

Acad. Sci. USA 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.,* gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.,* the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a xenogeneic polypeptide that comprises an polypeptide having substantial sequence identity, as described above, to the human polypeptide (also termed autologous antigen) which served as a reference polypeptide, but which xenogeneic polypeptide is derived from a different, non-human species. One skilled in the art will recognize that "self"antigens are often poor stimulators of CD8+ and CD4+ T-lymphocyte responses, and therefore efficient immunotherapeutic strategies directed against tumor polypeptides require the development of methods to overcome immune tolerance to particular self tumor polypeptides. For example, humans immunized with prostase protein from a xenogeneic (non human) origin are capable of mounting an immune response against the counterpart human protein, *e.g.* the human prostase tumor protein present on human tumor cells. Accordingly, the present invention provides methods for purifying the xenogeneic form of the tumor proteins set forth herein, such as the polypeptides set forth in SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554 and 4558-4560, or those encoded by polynucleotide sequences set forth in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452 and 454-4550.

Therefore, one aspect of the present invention provides xenogeneic variants of the polypeptide compositions described herein. Such xenogeneic variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity along their lengths, to a polypeptide sequences set forth herein.

More particularly, the invention is directed to mouse, rat, monkey, porcine and other non-human polypeptides which can be used as xenogeneic forms of human polypeptides set forth herein, to induce immune responses directed against tumor polypeptides of the invention.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may

assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may

generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a Mycobacterium sp., such as a Mycobacterium tuberculosis-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides,

at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the

development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of $CD4^+$ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.,* an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide

sequence set forth in any one of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, and 454-4550, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompasses homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length

between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like. A polynucleotide sequence as described here may be extended at one or both ends by additional nucleotides not found in the native sequence. This additional sequence may consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides at either end of the disclosed sequence or at both ends of the disclosed sequence.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* *5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* *4*:11-17; Robinson, E.D. (1971)

Comb. Theor 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of

the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the

desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are

provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller

fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will

typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski

et al., Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m, binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.,* Nucleic Acids Res. 1997, 25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a

hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA.

Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar

23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a

catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, Antisense Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE

mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, Science. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be

modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see

generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.,* expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR ™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as

LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from

the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to

generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site

located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the pBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or pSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as pBLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced;

pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J. 3*:1671-1680; Broglie, R. et al. (1984) *Science 224*:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the

polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired

fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci. 77*:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C.

Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a

nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol. 12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc. 85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunogically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in

the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d. See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as pancreatic cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To

determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* *6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the

preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "$F(ab')_2$ " fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using

recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H::V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some

FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeyen et al. (1988) Science 239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR

polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the

CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also

facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also

bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a

chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res. 54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

T Cell Receptor Compositions

The T cell receptor (TCR) consists of 2 different, highly variable polypeptide chains, termed the T-cell receptor α and β chains, that are linked by a disulfide bond (Janeway, Travers, Walport. Immunobiology. Fourth Ed., 148-159. Elsevier Science Ltd/Garland Publishing. 1999). The α/β heterodimer complexes with the invariant CD3 chains at the cell membrane. This complex recognizes specific antigenic peptides bound to MHC molecules. The enormous diversity of TCR specificities is generated much like immunoglobulin diversity, through somatic gene rearrangement. The β chain genes contain over 50 variable (V), 2 diversity (D), over 10 joining (J) segments, and 2 constant region segments (C). The α chain genes contain over 70 V segments, and over 60 J segments but no D segments, as well as one C segment. During T cell development in the thymus, the D to J gene rearrangement of the β chain occurs, followed by the V gene segment rearrangement to the DJ. This functional VDJβ exon is transcribed and spliced to join to a Cβ. For the α chain, a Vα gene segment rearranges to a Jα gene segment to create the functional exon that is then transcribed and spliced to the Cα. Diversity is further increased during the recombination process by the random addition of P and N-nucleotides between the V, D, and J segments of the β chain and between the V and J segments in the □ chain (Janeway, Travers, Walport. Immunobiology. Fourth Ed., 98 and 150. Elsevier Science Ltd/Garland Publishing. 1999).

The present invention, in another aspect, provides TCRs specific for a polypeptide disclosed herein, or for a variant or derivative thereof. In accordance with the present invention, polynucleotide and amino acid sequences are provided for the V-J or V-D-J junctional regions or parts thereof for the alpha and beta chains of the T-cell receptor which recognize tumor polypeptides described herein. In general, this aspect of the invention relates to T-cell receptors which recognize or bind tumor polypeptides presented in the context of MHC. In a preferred embodiment the tumor antigens recognized by the T-cell receptors comprise a polypeptide of the present invention. For example, cDNA encoding a TCR specific for a pancreatic tumor peptide can be isolated from T cells

specific for a tumor polypeptide using standard molecular biological and recombinant DNA techniques.

This invention further includes the T-cell receptors or analogs thereof having substantially the same function or activity as the T-cell receptors of this invention which recognize or bind tumor polypeptides. Such receptors include, but are not limited to, a fragment of the receptor, or a substitution, addition or deletion mutant of a T-cell receptor provided herein. This invention also encompasses polypeptides or peptides that are substantially homologous to the T-cell receptors provided herein or that retain substantially the same activity. The term "analog" includes any protein or polypeptide having an amino acid residue sequence substantially identical to the T-cell receptors provided herein in which one or more residues, preferably no more than 5 residues, more preferably no more than 25 residues have been conservatively substituted with a functionally similar residue and which displays the functional aspects of the T-cell receptor as described herein.

The present invention further provides for suitable mammalian host cells, for example, non-specific T cells, that are transfected with a polynucleotide encoding TCRs specific for a polypeptide described herein, thereby rendering the host cell specific for the polypeptide. The α and β chains of the TCR may be contained on separate expression vectors or alternatively, on a single expression vector that also contains an internal ribosome entry site (IRES) for cap-independent translation of the gene downstream of the IRES. Said host cells expressing TCRs specific for the polypeptide may be used, for example, for adoptive immunotherapy of pancreatic cancer as discussed further below.

In further aspects of the present invention, cloned TCRs specific for a polypeptide recited herein may be used in a kit for the diagnosis of pancreatic cancer. For example, the nucleic acid sequence or portions thereof, of tumor-specific TCRs can be used as probes or primers for the detection of expression of the rearranged genes encoding the specific TCR in a biological sample. Therefore, the present invention further provides for an assay for detecting messenger RNA or DNA encoding the TCR specific for a polypeptide.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell, TCR, and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody,TCR, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and theraputic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of

primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, *e.g.*, vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (*e.g.*, U.S. Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional

mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-274; Bett et al. (1993) J. Virol. 67:5911-5921; Mittereder et al. (1994) Human Gene Therapy 5:717-729; Seth et al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, *e.g.*, U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129; Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes

templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. J. Biol. Chem. (1993) 268:6866-6869 and Wagner et al. Proc. Natl. Acad. Sci. USA (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et

al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed

within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell, TCR, and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction

of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL® adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science 273*:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins . Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β-escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene

ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^{R} to increase viscosity, or may bc formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL® adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL® adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula

(I): $HO(CH_2CH_2O)_n$-A-R,

wherein, n is 1-50, A is a bond or –C(O)-, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein *n* is between 1 and 50,

preferably 4-24, most preferably 9; the *R* component is C_{1-50}, preferably C_4-C_{20} alkyl and most preferably C_{12} alkyl, and *A* is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12th edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.,* matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and

present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for

therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound,

such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems. such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

In another illustrative embodiment, calcium phosphate core particles are employed as carriers, vaccine adjuvants, or as controlled release matrices for the compositions of this invention. Exemplary calcium phosphate particles are disclosed, for example, in published patent application No. WO/0046147.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily

or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and

substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of

storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for

human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described, *e.g.,* in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts.

Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998 Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, he use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.,* Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

Immunologic approaches to cancer therapy are based on the recognition that cancer cells can often evade the body's defenses against aberrant or foreign cells and molecules, and that these defenses might be therapeutically stimulated to regain the lost ground, e.g. pgs. 623-648 in Klein, Immunology (Wiley-Interscience, New York, 1982). Numerous recent observations that various immune effectors can directly or indirectly inhibit growth of tumors has led to renewed interest in this approach to cancer therapy, e.g. Jager, et al., Oncology 2001;60(1):1-7; Renner, et al., Ann Hematol 2000 Dec;79(12):651-9.

Four-basic cell types whose function has been associated with antitumor cell immunity and the elimination of tumor cells from the body are: i) B-lymphocytes which secrete immunoglobulins into the blood plasma for identifying and labeling the nonself invader cells; ii) monocytes which secrete the complement proteins that are responsible for lysing and processing the immunoglobulin-coated target invader cells; iii) natural killer lymphocytes having two mechanisms for the destruction of tumor cells, antibody-dependent cellular cytotoxicity and natural killing; and iv) T-lymphocytes possessing antigen-specific receptors and having the capacity to recognize a tumor cell carrying

complementary marker molecules (Schreiber, H., 1989, in Fundamental Immunology (ed). W. E. Paul, pp. 923-955).

Cancer immunotherapy generally focuses on inducing humoral immune responses, cellular immune responses, or both. Moreover, it is well established that induction of $CD4^+$ T helper cells is necessary in order to secondarily induce either antibodies or cytotoxic $CD8^+$ T cells. Polypeptide antigens that are selective or ideally specific for cancer cells, particularly pancreatic cancer cells, offer a powerful approach for inducing immune responses against pancreatic cancer, and are an important aspect of the present invention.

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of pancreatic cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate

antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Monoclonal antibodies may be labeled with any of a variety of labels for desired selective usages in detection, diagnostic assays or therapeutic applications (as described in U.S. Patent Nos. 6,090,365; 6,015,542; 5,843,398; 5,595,721; and 4,708,930, hereby incorporated by reference in their entirety as if each was incorporated individually). In each case, the binding of the labelled monoclonal antibody to the determinant site of the antigen will signal detection or delivery of a particular therapeutic agent to the antigenic determinant on the non-normal cell. A further object of this invention is to provide the specific monoclonal antibody suitably labelled for achieving such desired selective usages thereof.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using

standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo.* Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.,* untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical

compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

<u>Cancer Detection and Diagnostic Compositions, Methods and Kits</u>

In general, a cancer may be detected in a patient based on the presence of one or more pancreatic tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as pancreatic cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a pancreatic tumor sequence should be present at a level that is at least two-fold, preferably three-fold, and more preferably five-fold or higher in tumor tissue than in normal tissue of the same type from which the tumor arose. Expression levels of a particular tumor sequence in tissue types different from that in which the tumor arose are irrelevant in certain diagnostic embodiments since the presence of tumor cells can be confirmed by

observation of predetermined tissue differential expression levels, e.g., 2-fold, 5-fold, etc, in tumor tissue to expression levels in normal tissue of the same type.

Other differential expression patterns can be utilized advantageously for diagnostic purposes. For example, in one aspect of thc invention, overexpression of a tumor sequence in tumor tissue and normal tissue of the same type, but not in other normal tissue types, *e.g.* PBMCs, can be exploited diagnostically. In this case, the presence of metastatic tumor cells, for example in a sample taken from the circulation or some other tissue site different from that in which the tumor arose, can be identified and/or confirmed by detecting expression of the tumor sequence in the sample, for example using RT-PCR analysis. In many instances, it will be desired to enrich for tumor cells in the sample of interest, e.g., PBMCs, using cell capture or other like techniques.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with

the immobilized binding agent. Suitable polypeptides for use within such assays include full length pancreatic tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with pancreatic cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An

appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as pancreatic cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain

methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or

probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another aspect of the present invention, cell capture technologies may be used in conjunction, with, for example, real-time PCR to provide a more sensitive tool for detection of metastatic cells expressing pancreatic tumor antigens. Detection of pancreatic cancer cells in biological samples, e.g., bone marrow samples, peripheral blood, and small needle aspiration samples is desirable for diagnosis and prognosis in pancreatic cancer patients.

Immunomagnetic beads coated with specific monoclonal antibodies to surface cell markers, or tetrameric antibody complexes, may be used to first enrich or positively select cancer cells in a sample. Various commercially available kits may be used, including Dynabeads® Epithelial Enrich (Dynal Biotech, Oslo, Norway), StemSep™

(StemCell Technologies, Inc., Vancouver, BC), and RosetteSep (StemCell Technologies). A skilled artisan will recognize that other methodologies and kits may also be used to enrich or positively select desired cell populations. Dynabeads® Epithelial Enrich contains magnetic beads coated with mAbs specific for two glycoprotein membrane antigens expressed on normal and neoplastic epithelial tissues. The coated beads may be added to a sample and the sample then applied to a magnet, thereby capturing the cells bound to the beads. The unwanted cells are washed away and the magnetically isolated cells eluted from the beads and used in further analyses.

RosetteSep can be used to enrich cells directly from a blood sample and consists of a cocktail of tetrameric antibodies that targets a variety of unwanted cells and crosslinks them to glycophorin A on red blood cells (RBC) present in the sample, forming rosettes. When centrifuged over Ficoll, targeted cells pellet along with the free RBC. The combination of antibodies in the depletion cocktail determines which cells will be removed and consequently which cells will be recovered. Antibodies that are available include, but are not limited to: CD2, CD3, CD4, CD5, CD8, CD10, CD11b, CD14, CD15, CD16, CD19, CD20, CD24, CD25, CD29, CD33, CD34, CD36, CD38, CD41, CD45, CD45RA, CD45RO, CD56, CD66B, CD66e, HLA-DR, IgE, and TCRαβ.

Additionally, it is contemplated in the present invention that mAbs specific for pancreatic tumor antigens can be generated and used in a similar manner. For example, mAbs that bind to tumor-specific cell surface antigens may be conjugated to magnetic beads, or formulated in a tetrameric antibody complex, and used to enrich or positively select metastatic %%% tumor cells from a sample. Once a sample is enriched or positively selected, cells may be lysed and RNA isolated. RNA may then be subjected to RT-PCR analysis using %%% tumor-specific primers in a real-time PCR assay as described herein. One skilled in the art will recognize that enriched or selected populations of cells may be analyzed by other methods (*e.g. in situ* hybridization or flow cytometry).

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of

reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

SEQ ID NOs of the instant application claim priority according to the following:

Application 60/265,305	filed January 30, 2001	SEQ ID NOs:1-74	566P1
Application 60/305,484	filed July 12, 2001	SEQ ID NOs:75-453	566P2
Application 60/333,626	filed November 27, 2001	SEQ ID NOs:454-455	566P3
Application 60/267,568	filed February 9, 2001	SEQ ID NOs:456-528	570P1
Application 60/265,682	filed January 31, 2001	SEQ ID NOs:529-4272	567P1
Application 60/278,651	filed March 21, 2001	SEQ ID NOs:4273-4345	567P2
Application 60/287,121	filed April 27, 2001	SEQ ID NOs:4346-4546	567P3
Application 60/313,999	filed August 20, 2001	SEQ ID NOs:4547-4554	567P5

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

IDENTIFICATION OF PANCREATIC TUMOR PROTEIN CDNAS FROM A PCR-BASED SUBTRACTION LIBRARY.

This Example discloses the isolation and identification of cDNA molecules from a cDNA library enriched in polynucleotides encoding secreted and transmembrane proteins.

A cDNA library was constructed by the method of Kopcznski *et al.* from mRNA purified from rough endoplasmic reticulum (RER) isolated from primary pancreatic tumor cells (PANC 391-34). *Proc. Natl. Acad. Sci.* 95:9973-9978 (1998) (incorporated herein by reference in its entirety). Briefly, cDNA was prepared from isolated mRNA by employing standard methodology. *See, e.g.*, Ausubel *et al.*, "Short Protocols in Molecular Biology" (4^{th} ed., 1999). The resulting cDNAs were ligated into a LAMBDA ZAP EXPRESS™ vector (Stratagene; La Jolla, California) and mass excision was then employed to generate a plasmid library in *E. coli*. Individual *E. coli* colonies were isolated and the cDNA clones subjected to nucleic acid sequencing. The nucleotide sequences of exemplary clones are disclosed herein as SEQ ID NOs:1-66, 75-152, 174-177, 182, 184-452, 454-4550. The predicted amino acid sequences of these clones are presented as SEQ ID NOs:67-74, 153-173, 178-181, 183, 453, 4551-4554 and 4558-4560.

A cDNA library was also constructed and cloned into the PCR2.1 vector (Invitrogen, Carlsbad, CA) by subtracting a pool of one or more tumor cDNAs with a pool of cDNA from normal tissues, for example, colon, spleen, brain, liver, kidney, lung, stomach and small intestine, using PCR subtraction methodologies (Clontech, Palo Alto, CA). The subtraction is performed using a PCR-based protocol, which is modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA are separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion results in an average

cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification does not affect the subtraction efficiency. Two tester populations are then created with different adapters, and the driver library remains without adapters.

The tester and driver libraries are then hybridized using excess driver cDNA. In the first hybridization step, driver is separately hybridized with each of the tester cDNA populations. This results in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs, and (d) unhybridized driver cDNAs. The two separate hybridization reactions are then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) is generated in which tester cDNA with one adapter is hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step results in enrichment of differentially expressed sequences which can be used as templates for PCR amplification with adapter-specific primers. The ends are then filled in, and PCR amplification is performed using adapter-specific primers. Only population (e), which contained tester cDNA that do not hybridize to driver cDNA, are amplified exponentially. A second PCR amplification step is then performed, to reduce background and further enrich differentially expressed sequences. This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are over-expressed in pancreatic tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

EXAMPLE 2

ANALYSIS OFcDNA EXPRESSION OF PANCREATIC TUMOR CDNAS USING MICROARRAY TECHNOLOGY

To determine mRNA expression levels of the isolated cDNA clones, cDNA clones from the pancreatic tumor subtraction library were randomly picked and colony

PCR amplified. Their mRNA expression levels in pancreatic tumor, normal pancreas and various other normal tissues were determined using microarray technology (Rosetta Inpharmatics, Inc., Kirkland, WA). Briefly, the PCR amplification products were arrayed onto slides into an array format, with each product occupying a unique location in the array. To do this, mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. Data was analyzed using software provided by the manufacturer.

In additional studies, sequences disclosed herein were evaluated for overexpression in specific tumor tissues by microarray analysis. Using this approach, clones from the cDNA library described in Example 1 were randomly picked, PCR amplified, and their mRNA expression profiles in tumor and normal tissues were examined using cDNA microarray technology essentially as described (Shena, M. *et al.*, 1995 Science *270*:467-70). In brief, the clones were arrayed onto glass slides as multiple replicas, with each location corresponding to a unique cDNA clone (as many as 5500 clones can be arrayed on a single slide, or chip). Each chip was hybridized with a pair of cDNA probes that were fluorescence-labeled with Cy3 and Cy5, respectively. Typically, 1 μg of polyA$^+$ RNA was used to generate each cDNA probe. After hybridization, the chips were scanned and the fluorescence intensity recorded for both Cy3 and Cy5 channels. There were multiple built-in quality control steps. First, the probe quality was monitored using a panel of ubiquitously expressed genes. Secondly, the control plate also included yeast DNA fragments of which complementary RNA may be spiked into the probe synthesis for measuring the quality of the probe and the sensitivity of the analysis. Currently, the technology offers a sensitivity of 1 in 100,000 copies of mRNA. Finally, the reproducibility of this technology was ensured by including duplicated control cDNA elements at different locations.

Those cDNAs showing at least two-fold overexpression in tumor samples as compared to normal samples, and/or demonstrating overexpression based on visual analysis of the microarray data, were searched against Genbank and the results are shown

in Table 2. These sequences are set forth in SEQ ID NOs:75-129. Full-length cDNA and protein sequences for 28 of these clones are dislosed in SEQ ID NOs:130-183 and are shown in Table 3.

TABLE 2

Microarray and Genbank Search Results for Pancreas cDNAs

SEQ ID NO:	Element (384	Well 384	Plate:well 96	Pancrease Chip 2 Microarray Data				Blastn
				Clone ID	Ratio	Median Signal 1	Median Signal 2	
75	PCX352 _r01c15	a 15	838:A8	80150	2.37	0.648	0.273	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
76	PCX352_ r01c16	a 16	838:B8	80151	1.88	0.292	0.156	Hu. serine (or cysteine) proteinase inhibitor, clade E
77	PCX352_ r01c23	a 23	838:A12	80152	1.83	0.906	0.496	Hu. keratin 18 (KRT18)
78	PCX352_ r03c11	c 11	838:E6	80153	1.06	0.481	0.456	Hu. Rab geranylgeranyltransferase, beta subunit (RABGGTB)
79	PCX352_ r04c03	d 3	838:G2	80154	1.06	0.193	0.183	Hu. FAT tumor suppressor (Drosophila) homolog (FAT)
80	PCX352_ r04c11	d 11	838:G6	80155	1.55	0.999	0.645	Hu. mRNA for transmembrane protein (THW gene), p53-induced protein PIGPC1 (PIGPC1)
81	PCX352_ r07c03	g 3	839:E2	80156	0.95	0.253	0.266	Hu. fibrillarin (FBL)
82	PCX352_ r08c06	h 6	839:H3	80157	0.76	0.273	0.359	Hu. fibrillarin (FBL)
83	PCX352_ r10c16	j 16	840:D8	80158	2.75	0.937	0.34	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
84	PCX352_ r10c24	j 24	840:D12	80159	5.14	3.94	0.767	Hu. similar to collagen, type I, alpha 1; Collagen I, alpha-1 polypeptide

SEQ ID NO:	Element (384	Well 384	Plate:well 96	Pancrease Chip 2 Microarray Data Clone ID	Ratio	Median Signal 1	Median Signal 2	Blastn
85	PCX352_r12c04	l 4	840:H2	80161	1.89	0.51	0.27	Hu. serine (or cysteine) proteinase inhibitor, clade E
86	PCX352_r12c07	l 7	840:G4	80162	0.77	0.314	0.407	Hu. pM5 protein (PM5)
87	PCX352_r12c20	l 20	840:H10	80163	1.55	0.72	0.466	Hu. fibrillarin (FBL)
88	PCX352_r15c03	o 3	841:E2	80164	1.5	0.178	0.119	Hu. type I transmembrane receptor (seizure-related protein)(PSK-1)
89	PCX352_r15c17	o 17	841:E9	80165	2.14	1.219	0.568	Hu. CD24 antigen (small cell lung carcinoma cluster 4antigen) (CD24)
90	PCX352_r16c08	p 8	841:H4	80166	0.59	0.192	0.329	Hu. fibrillarin (FBL)
91	PCX353_r01c03	a 3	842:A2	80167	2.68	0.071	0.027	Hu. highly similar to glucose-6-phosphate dehydrogenase; ubiquitin-like protein (GdX)
92	PCX353_r02c11	b 11	842:C6	80168	2.87	1.156	0.403	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
93	PCX353_r02c23	b 23	842:C12	80169	2.72	1.001	0.368	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
94	PCX353_r06c08	f 8	843:D4	80170	1.84	1.602	0.87	Hu. keratin 18 (KRT18)
95	PCX353_r07c22	g 22	843:F11	80171	1.6	0.588	0.368	Hu. plastin 3 (T isoform) (PLS3)
96	PCX353_r08c06	h 6	843:H3	80173	1.55	0.378	0.244	Hu. liver-specific bHLH-Zip transcription factor (LISCH7)

				Pancrease Chip 2 Microarray Data				
SEQ ID NO:	Element (384	Well 384	Plate:well 96	Clone ID	Ratio	Median Signal 1	Median Signal 2	Blastn
97	PCX353_r13c20	m 20	845:B10	80175	1.22	0.26	0.214	Hu. collagen, type XVIII, alpha 1 (COL18A1)
98	PCX353_r13c23	m 23	845:A12	80176	1.59	0.432	0.272	Hu. tissue factor pathway inhibitor 2 (TFPI2), placental protein 5 (PP5)
99	PCX353_r16c10	p 10	845:H5	80178	1.72	1.116	0.649	Hu. tumor antigen (L6)
100	PCX354_r01c03	a 3	846:A2	80180	1.57	0.095	0.06	Hu. small EDRK-rich factor 1B (centromeric) (SERF1B)
101	PCX354_r03c02	c 2	846:F1	80181	1.8	0.951	0.53	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
102	PCX354_r04c04	d 4	846:H2	80183	1.17	0.301	0.258	Hu. fibrillarin (FBL)
103	PCX354_r04c10	d 10	846:H5	80184	1.76	0.545	0.31	Hu. BAC clone RP11-549B18 from 18
104	PCX354_r05c14	e 14	847:B7	80185	2	1.475	0.739	Hu. tumor antigen (L6)
105	PCX354_r05c21	e 21	847:A11	80186	3.6	1.049	0.291	Novel (short/ poor sequence)
106	PCX354_r08c03	h 3	847:G2	80187	3.03	0.335	0.11	Hu. thrombospondin 2 (THBS2)
107	PCX354_r08c14	h 14	847:H7	80188	1.58	1.032	0.654	Hu. clone RP11-527G2, DKFZP564A2416 protein
108	PCX354_r08c23	h 23	847:G12	80189	2.38	1.421	0.596	Hu. tumor antigen (L6)
109	PCX354_r09c15	i 15	848:A8	80191	2.44	0.602	0.247	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
110	PCX354_r09c19	i 19	848:A10	80192	2.22	0.753	0.339	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)

SEQ ID NO:	Element (384	Well 384	Plate:well 96	Clone ID	Ratio	Median Signal 1	Median Signal 2	Blastn
				Pancrease Chip 2 Microarray Data				
111	PCX354_r11c13	k 13	848:E7	80193	2	0.391	0.196	Hu. sema domain, immunoglobulin domain (Ig), short basicdomain, secreted, (semaphorin) 3C (SEMA3C)
112	PCX354_r11c19	k 19	848:E10	80194	2.2	1.718	0.783	Hu. connective tissue growth factor (CTGF)
113	PCX354_r12c15	l 15	848:G8	80195	2.15	1.144	0.533	Hu. p53-induced protein PIGPC1, transmembrane protein (THW gene)
114	PCX355_r01c03	a 3	850:A2	80196	1.79	0.092	0.051	Human mitochondrion
115	PCX355_r02c11	b 11	850:C6	80197	1.96	1.442	0.735	Hu. connective tissue growth factor (CTGF)
116	PCX355_r07c23	g 23	851:E12	80198	1.91	1.295	0.679	Hu. keratin 18 (KRT18)
117	PCX355_r10c23	j 23	852:C12	80199	1.68	0.823	0.489	Hu. keratin 18 (KRT18)
118	PCX353_r08c01	h 1	843:G1	80172	1.65	0.482	0.291	Hu. serine (or cysteine) proteinase inhibitor, clade E
119	PCX353_r10c11	j 11	844:C6	80174	1.45	0.412	0.285	Hu. FAT tumor suppressor (Drosophila) homolog (FAT)
120	PCX353_r15c02	o 2	845:F1	80177	1.05	0.47	0.446	Hu. similar to heterochromatin-like protein 1
121	PCX353_r16c16	p 16	845:H8	80179	1.76	1.259	0.715	Hu. transmembrane protein (THW gene), PIGPC1
122	PCX354_r09c03	i 3	848:A2	80190	2.35	0.789	0.336	Hu. p53-induced protein PIGPC1, transmembrane protein (THW g

SEQ ID NO:	Element (384	Well 384	Plate:well 96	Pancrease Chip 2 Microarray Data: Clone ID	Ratio	Median Signal 1	Median Signal 2	Blastn
123	PCX355_r11c11	k 11	852:E6	80200	1.9	0.881	0.463	Hu. tumor antigen (L6)
124	PCX355_r15c13	o 13	853:E7	80201	1.67	0.414	0.248	Hu. stearoyl-CoA desaturase (SCD)
125	PCX356_r03c06	c 6	854:F3	80203	1.58	0.59	0.373	Hu. chromogranin B (secretogranin 1)
126	PCX356_r04c20	d 20	854:H10	80204	3.1	0. 062	0.02	Hu. serine (or cysteine) proteinase inhibitor, clade E
127	PCX356_r06c11	f 11	855:C6	80205	2.01	1.117	0.556	Hu. tumor antigen (L6), transmembrane 4 superfamily member 1
128	PCX356_r07c24	g 24	855:F12	80207	1.69	0.301	0.178	Novel - short sequence
129	PCX356_r12c21	l 21	856:G11	80208	1.5	0. 254	0.169	Hu. Fer-1 (C. elegans)-like 3 (myoferlin)

TABLE 3

Full-length cDNA and Protein sequences for Pancreas cDNAs

SEQ ID NO: (Full-Length cDNA/Pro)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
130/153	IodesPancChip2-1	80150	Hu.p53-induced protein PICPC1, transmembrane protein (THW gene)
131/154	IodesPancChip2-2	80151	Hu.serine (or cysteine) proteinase inhibitor, clade E
132/155	IodesPancChip2-3	81052	Hu.keratin 18 (KRT18)
133/156	IodesPancChip2-4	81053	Hu.Rab geranylgeranyltransferase, beta subunit (RABGGTB)

SEQ ID NO: (Full-Length cDNA/Pro)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
134/157	IodesPancChip2-5	81054	Hu.FAT tumor suppressor (Drosophila) homolog (FAT)
135/158	IodesPancChip2-7	80156	Hu.fibrallarin (FBL)
136/159	IodesPancChip2-10	80159	Hu.similar to collagen, type I, alpha 1; Collagen I, alpha-1 polypeptide
137/160	IodesPancChip2-13	80162	Hu.pM5 protein (PM5)
138/161	IodesPancChip2-15	80164	Hu.type I transmembrane receptor (seizure-related protein) (PSK-1)
139/162	IodesPancChip2-16	80165	Hu.CD24 antigen (small cell lung carcinoma cluster 4antigen) (CD24)
140	IodesPancChip2-18	80167	Hu.highly similar to glucose-6-phosphate dehydrogenase
141/163		80167	Hu. ubiquitin-like protein (GdX)
142/164	IodesPancChip2-22	80171	Hu. plastin 3 (T isoform) (PLS3)
143/165	IodesPancChip2-24	80173	Hu. liver-specific bHLH-Zip transcription factor (LISCH7)
144/166	IodesPancChip2-26	80175	Hu. collagen, type XVIII, alpha 1 (COL18A1)
145/167	IodesPancChip2-27	80176	Hu. tissue factor pathway inhibitor 2 (TFPI2), placental protein 5 (PP5)
146/168	IodesPancChip2-29	80178	Hu. tumor antigen (L6)
147/169	IodesPancChip2-31	80180	(SERF1A)
148/170	LodesPancChip2-31	80180	Hu.small EDRK-rich factor 1B (centromeric) (SERF1B)
149/171	IodesPancChip2-38	80187	Hu.thrombospondin 2 (THBS2)
150/172	IodesPancChip2-44	80193	Hu.sema domain, immunoglobulin domain (lg), short basicdomain, secreted, (semaphorin) 3C (SEMA3C)

SEQ ID NO: (Full-Length cDNA/Pro)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
151/173	IodesPancChip2-45	80194	Hu.connective tissue growth factor (CTGF)
152	IodesPancChip2-47	80196	Human pHL-1 gene, c-myc oncogene containing coxIII sequence
174/178	IodesPancChip2-28	80177	Heterochromatin-like protein 1
175/179	IodesPancChip2-52	80201	Hu. stearoyl-CoA desaturase (SCD)
176/180	IodesPancChip2-54	80203	Hu. chromogranin B (secretogranin 1)
177/181	IodesPancChip2-59	80208	Hu. Fer-1 (C.elegans)-like 3 (myoferlin)
182/183	IodesPancChip2-11	80160	Hu. clone MGC:15409; 93% homolgy to NF-IL6

EXAMPLE 3

IDENTIFICATION OF ADDITIONAL PANCREATIC TUMOR PROTEIN CDNAS FROM AN EXPRESSION LIBRARY

The PCR-based subtraction library described in Example 1 was further screened to isolate additional cDNAs expressed in pancreatic tumor cells. An additional 268 clones were identified and are disclosed in SEQ ID NOs:184-452. The clones were sequenced and the sequences used in a BLAST search against Genbank. Those sequences showing some degree of similarity to sequences in Genbank are described in Table 4. Those sequences showing no significant similarity to sequences in Genbank are listed in Table 5.

TABLE 4

Pancreas Tumor Sequences Showing Some Degree of Similarity to Sequences in Genbank

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
185	PNCM-2	71232	Hu. putative ionotropic glutamate receptor GLURR2
186	PNCM-3	71233	Hu. accessory proteins BAP31/BAP29, 6C6-Ag, CDM
188	PNCM-5	71235	Hu. prosaposin (PSAP), sphingolipid activator protein 1
189	PNCM-6	71236	Hu.similar to adaptor-related protein complex 3, sigma 2subunit
			Hu.alanyl (membrane) aminopeptidase (aminopeptidase N)
190	PNCM-7	71237	Hu.prosaposin
191	PNCM-8	73408	Hu. ribosome binding protein 1, ES/130
192	PNCM-9	73409	Hu. kinectin 1 (kinesin receptor) (KTN1)
193	PNCM-11	73410	Hu. Protein A kinase (PPKA) anchor protein (gravin) 12

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
194	PNCM-12	71238	Hu.golgi autoantigen, golgin subfamily a, 4 (GOLGA4)
195	PNCM-13	73411	Hu. kinectin 1 (kinesin receptor) (KTN1)
196	PNCM-14	71239	Hu.prosaposin
197, 198	PNCM-15	73412	Hu.prosaposin
199	PNCM-16	71240	Hu.prosaposin
200	PNCM-18	71241	Hu.prosaposin
201	PNCM-19	71242	Hu.centromere protein F (350/400kD, mitosin) (CENPF)
202	PNCM-20	73413	Hu. lamin A/C (nuclear env. protein)
203	PNCM-21	71243	Hu.prosaposin
204	PNCM-22	71244	Hu.prosaposin
205	PNCM-23	71245	Hu.methyl-CpG binding domain protein 2 (MBD2)
206	PNCM-24	71246	Hu.prosaposin
207	PNCM-25	71247	Hu.prosaposin
208	PNCM-26	71248	Hu.prosaposin
209	PNCM-27	71249	Hu. E3 ubiquitin ligase SMURF2
210	PNCM-28	73414	Hu.Kinectin 1
211	PNCM-29	71250	Hu.fer-1 (C.elegans)-like 3 (myoferlin) (FER1L3)
214	PNCM-32	71253	Hu.ECSIT (Toll/IL-1 signal transduction)
215	PNCM-33	71254	Hu. villin 2, cytovillin 2, (ezrin) (VIL2)
216, 217	PNCM-34	71255	Hu.mitotic checkpoint protein isoform MAD1a (MAD1)
218	PNCM-35	71256	Hu.Homer-2A
219	PNCM-36	73415	Macaca fascicularis brain cDNA, clone:QflA-11332
220	PNCM-37	71257	Hu. prosaposin
221	PNCM-38	71258	Hu.methyl-CpG binding domain protein 2 (MBD2)
222	PNCM-39a	71259	Hu. lamin A/C (nuclear env. protein)
223	PNCM-39b	73416	Hu. sphingolipid activator proteins 1 and 2 processedmutant

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
224	PNCM-40	71260	Hu. rabaptin-5 (RAB5EP) (endocytic transport)
225	PNCM-41	73376	Hu.fer-1
226	PNCM-42	73377	Hu.CD36 antigen-like 2, lysosomal sialoglycoprotein
227	PNCM-43	73378	Hu. Protein A kinase (PPKA) anchor protein (gravin) 12
228	PNCM-44	73379	Hu. Prosaposin
229, 230	PNCM-47	73381	Hu. mitochondrion
231	PNCM-48	73382	Hu.vimentin (VIM)
232, 233	PNCM-49	73383	Hu.hydroxysteroid (17-beta) dehydrogenase 4
234, 235	PNCM-50	73384	Hu.amyloid beta (A4) precursor-like protein 2 (APLP2)
236	PNCM-51	73385	Hu.Ran binding protein 2
237	PNCM-53	73386	Hu.alanyl (membrane) aminopeptidase (aminopeptidase N)
238	PNCM-56	73387	Hu. kinectin 1 (kinesin receptor) (KTN1)
239, 240	PNCM-57	73388	Hu. kinectin 1(Reverse orientation)
241, 242	PNCM-58	73389	Hu.vimentin (VIM)
243	PNCM-59	73390	Hu. glutahione-S-transferase like; glutahionetransferase omega
244	PNCM-60	73391	Hu. ribosome binding protein 1, ES/130, KIAA 1398
245	PNCM-61	73417	Hu.Ran binding protein 2
246	PNCM-62	73392	Hu. putative ionotropic glutamate receptor GLURR2
247	PNCM-63	73393	Hu.fer-1 (C.elegans)-like 3 (myoferlin) (FER1L3)
248	PNCM-65	73418	Hu. transferrin receptor (p90, CD71) (TFRC)
249	PNCM-66	73395	Hu. ribosome binding protein 1, ES/130, KIAA 1398
250	PNCM-67	73396	Hu.Similar to glucose regulated protein, 58kDa, cloneMGC:3178
251	PNCM-68	73397	Hu. kinectin 1 (kinesin receptor) (KTN1)

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
252, 253	PNCM-69	73419	Hu.cDNA FLJ10480 fis, clone NT2RP2000126
254	PNCM-70	73398	Hu. kinectin 1 (kinesin receptor) (KTN1)
255,256	PNCM-71	73399	Hu.TATA element modulatory factor 1 (TMF1)
257	PNCM-72	73400	Hu. enoyl Coenzyme A hydratase 1, peroxisomal (ECH1)
258, 259	PNCM-73	73420	Hu.prosaposin
260	PNCM-74	73401	Hu.vimentin (VIM) [bp]
261	PNCM-77	73404	Hu.prosaposin
262	PNCM-78	73405	Hu.golgi autoantigen, golgin subfamily a, 4 (GOLGA4)
263, 264	PNCM-80	73407	Hu. kinectin 1 (kinesin receptor) (KTN1)
265	PNCM-81	72174	Hu.ribosomal protein L9
266	PNCM-82	72175	Hu.putative transmembrane protein
267	PNCM-83	72176	Hu. kinectin 1 (kinesin receptor) (KTN1)
268	PNCM-84	72177	Hu.prosaposin
269	PNCM-85	72178	Hu. ORF (LOC51035) w/CpGIsland and Ubiq.-binding domains
270	PNCM-86	72179	Hu. Protein A kinase (PRKA) anchor protein (gravin) 12 (AKAP12)
271, 272	PNCM-87	73421	Hu. heat shock 105kD, antigen NY-CO-25
273	PNCM-88	72180	Hu. heat shock 105kD, antigen NY-CO-25(Colon cancer Ag.)
274	PNCM-89	72181	Hu. ferritin, heavy polypeptide 1 (FTH1)
275	PNCM-90	72182	Hu.frizzled (Drosophila) homolog 6 (FZD6)
276	PNCM-91	72183	Hu.vimentin (VIM)
277	PNCM-92	72184	Hu.Ran binding protein 2 [bp198-610], sperm membrane protein BS-63, nucleoporin (NUP358)
278	PNCM-93	72185	Hu. kinectin 1 (kinesin receptor) (KTN1)
279	PNCM-94	72186	Hu.Tax-1 (T-cell leukemia virus type I) bindingprotein 1 (TAX1BP1) [bp 923-1335]; TRAF6-binding protein T6BP (IL-1 signaling)
280	PNCM-95	72187	Hu. kinectin 1 (kinesin receptor) (KTN1) [bp 813-

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
			1223]
281	PNCM-96	72188	Hu.prosaposin [bp 608-1018]
282	PNCM-97	72189	Hu.heat shock 105kD…[bp 1-412]
283	PNCM-98	72190	Hu. clone IMAGE:3449323
284	PNCM-99	72191	Hu. rabaptin-5 [bp1578-1990]
285	PNCM-100	72192	Hu.TNF receptor-1 associated protein (TRADD)
286	PNCM-101	72193	Hu.trans-Golgi network protein
287	PNCM-102	72194	Hu.IMAGE:3355762, chromodomain helicase DNA binding protein 1-like
288	PNCM-103	72195	Hu. ribosome binding protein 1, ES/130 [bp1563-1975], KIAA1398
289	PNCM-106	72196	Hu.ubiquinol-cytochrome c reductase core protein II (UQCRC2)
290	PNCM-110	72197	Hu. ribosome binding protein 1, ES/130 [bp717-1129], KIAA1398
291	PNCM-112	72198	Hu.accessory proteins BAP31/BAP29 [bp237-648], 6C6-Ag, CDM
292	PNCM-113	72199	Hu.M-phase phosphoprotein 1 (MPHOSPH1)
293	PNCM-114	72200	Hu. serine palmitoyltransferase, subunit I (enzyme in sphingolipid biosynth.)
294	PNCM-115	72201	Hu. kinectin 1 (kinesin receptor) (KTN1)[bp 1896-2306]
295	PNCM-116	72202	Hu.Tax-1 [bp 1-380]
296	PNCM-117	72203	Hu. methyl-CpG binding domain protein 2 (MDB2)
297	PNCM-118	72204	Hu. cDNA: FLJ23027 fis, clone LNG01826
298	PNCM-119	72205	Hu. cDNA DKFZp586F1918
299, 300	PNCM-120	72206	Macaca fascicularis brain cDNA, clone QflA-11332
301	PNCM-122	73422	Hu.heat shock 105kD, antigen NY-CO-25
302	PNCM-123	73423	Hu.IMAGE:3355762, chromodomain helicase DNA binding protein 1-like
303	PNCM-124	73424	Hu. kinectin 1 (kinesin receptor) KTN1) [bp]
304, 305	PNCM-125	73425	Hu.vimentin (VIM) [bp]

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
306	PNCM-126	74597	Hu.prosaposin
307, 308	PNCM-128	73426	Hu. cleavage stimulation factor,subunit 3, 77kD(CSTF3)
309, 310	PNCM-129	73427	Hu.diazepam binding inhibitor (GABA receptor modulator,acyl-Coenzyme A binding protein)
311	PNCM-131	73428	Hu.prosaposin
312	PNCM-132	73429	Hu., Similar to glucose regulated protein, 58kDa, cloneMGC:3178
313, 314	PNCM-133	74598	Hu. kinectin 1 (kinesin receptor) (KTN1)
315	PNCM-134	74599	Hu.prosaposin
316	PNCM-135	73430	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
317, 318	PNCM-136	74600	Hu. ferritin, heavy polypeptide 1 (FTH1)
319, 320	PNCM-137	74601	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
321, 322	PNCM-138	73437	Hu. RER1 protein (RER1)
323, 324	PNCM-139	73438	Hu.prosaposin
325, 326	PNCM-141	73439	Hu.Tax-1(T-cell leukemia virus type I) bindingprotein (TAX1BP1)
327, 328	PNCM-142	73440	Hu. Protein A kinase (PRKA) anchor protein (gravin) 12
329	PNCM-143	73441	Hu.prosaposin
330, 331	PNCM-144	73442	Hu.prosaposin
332, 333	PNCM-145	73443	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
336	PNCM-147	74602	Hu.fer-1 (C.elegans)-like 3 (myoferlin) (FER1L3)
337	PNCM-148	73445	Hu.prosaposin (PSAP),sphingolipid activator protein 1
338	PNCM-150	73456	Hu.heat shock 105kD,antigen NY-CO-25
339	PNCM-151	73585	Hu. heat shock 105kD (HSP-105B)
340, 341	PNCM-152	73586	Hu. Protein A kinase (PRKA) anchor protein (gravin) 12

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
342, 343	PNCM-153	73587	Hu. cleavage stimulation factor,subunit 3, 77kD(CSTF3)
344, 345	PNCM-154	73457	Hu.methyl-CpG binding domain protein 2 (MBD2)
346, 347	PNCM-155	74603	Hu. Protein A kinase (PRKA) anchor protein (gravin) 12
348	PNCM-157	73458	Hu. Protein A kinase (PRKA) anchor protein (gravin) 12
349, 350	PNCM-158	73459	Hu.low density lipoprotein-related protein-associated protein 1
351, 352	PNCM-159	73460	Hu.prosaposin
353	PNCM-160	73461	Hu.accessory proteins BAP31/BAP29 [bp155-662],6C6-Ag,CDM
354, 355	PNCM-161	74604	Hu. cleavage stimulation factor,subunit 3, 77kD(CSTF3)
356, 357	PNCM-162	74605	Hu.prosaposin, Hu.Tax-1
358, 359	PNCM-163	74606	Hu.leucine zipper-EF-hand containing transmembrane protein 1 (LETM1)
360, 361	PNCM-164	74607	Hu.CD36 antigen-like 2, lysosomal sialoglycoprotein
362, 363	PNCM-165	74608	Hu.prosaposin
364	PNCM-167	74610	Hu.transmembrane protein (63kD)
365	PNCM-169	74611	Hu.IMAGE:3355762,FLJ22530 fis, clone HRC12866,Hu.prosaposin, Hu.Tax-1
366, 367	PNCM-171	74613	Hu.leucine rich repeat (in FLII) interacting protein 1(LRRFIP1)
368, 369	PNCM-172	74614	Hu.prosaposin
370, 371	PNCM-173	74640	Hu.prosaposin
372, 373	PNCM-174	74615	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
374, 375	PNCM-175	74616	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
376	PNCM-176	74617	Hu.prosaposin
377	PNCM-177	77101	Hu. cleavage stimulation factor subunit 3

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
			77kD(CSTF3)
378	PNCM-178	77102	Hu. Protein Protein A kinase (PRKA) anchor protein (gravin) 12
379	PNCM-180	77104	Hu.prosaposin
380, 381	PNCM-182	74618	Hu.prosaposin
382	PNCM-183	74619	Hu.Ran binding protein 2, sperm membrane protein BS-63, nucleoporin
383, 384	PNCM-185	74620	Hu.prosaposin
385, 386	PNCM-186	74621	Hu. ribosome binding protein 1,KIAA1398,clone RP11-462D18(5-prime)
387, 388	PNCM-188	74623	Hu.IMAGE:3355762,FLJ22530 fis, clone HRC12866
389, 390	PNCM-189	74624	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
391, 392	PNCM-190	74625	Hu.Ran binding protein 2, sperm membrane protein BS-63, nucleoporin
393	PNCM-191	74631	Hu.diazepam binding inhibitor (GABA receptor modulator,acyl-Coenzyme A binding protein)
394, 395	PNCM-193	74632	Hu. endozepine, vimentin
396	PNCM-202	77105	Hu. glucose-regulated protein, 58kD (GRP58)
397	PNCM-208	77108	Hu. rabaptin-5 (RAB5EP)
398	PNCM-210	77109	Hu.vimentin (VIM)
399	PNCM-215	77114	Hu. hypothetical protein FLJ10634, clone MGC:944
400	PNCM-219	77118	Hu.alanyl (membrane) amineopeptidase (aminopeptidase N)
401	PNCM-221	77120	Hu.similar to RAN binding protein 2 [bp 576...],nucleoporin (NUP358), sperm-binding protein
402	PNCM-223	77122	Hu. cell surface glycoprotein/ cell adhesion molecule CD44
403	PNCM-224	77123	Hu.sperm membrane protein BS-63, RANBP2
404	PNCM-226	77125	Hu. Protein Protein A kinase (PRKA) anchor

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
			protein (gravin) 12
405	PNCM-229	77127	Prosaposin
406	PNCM-231	77129	Hu. Vimentin
407	PNCM-232	77130	Prosaposin
408	PNCM-234	77132	Prosaposin
409	PNCM-237	77134	Hu. Vimentin
410	PNCM-238	77135	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
411	PNCM-239	77136	Hu. ribosomal protein P0
412	PNCM-243	77139	Hu. rabaptin-5 (RAB5EP)
413	PNCM-244	77140	Prosaposin
414	PNCM-245	77141	Hu.,Similar to glucose regulated protein, 58 kDa, cloneMGC:3178
415	PNCM-248	77144	Hu. ORF (LOC51035);Similar to ORF, clone MGC:2274; clone MGC:5321
416	PNCM-250	77146	Hu.accessory proteins BAP31/BAP29[bp404],6C6-Ag,CDM
417	PNCM-253	77149	Hu. methyl-CpG binding domain protein 2 (MBD2)
418	PNCM-258	77474	Hu. Sim.to glucose-reg.protein[bp1-99];60bp: cGMP-specific phosphodiesterase
419	PNCM-266	77153	Hu.fer-1 (C.elegans)-like 3 (myoferlin) (FER1L3)
420	PNCM-267	77479	Hu. Kinectin 1
421	PNCM-268	77154	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
422	PNCM-269	77155	Hu. Kinectin 1
423	PNCM-271	77157	Hu. Kinectin 1
424	PNCM-272	77480	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
425	PNCM-278	77485	Prosaposin
426	PNCM-282	77487	Hu.methyl-CpG binding domain protein 2 (MBD2),antigen NY-CO-41

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
427	PNCM-283	77488	Hu. Kinectin 1
428	PNCM-287	77490	Hu. Kinectin 1
429	PNCM-293	77494	Hu. ribosome binding protein 1, ES/130
430	PNCM-294	77495	Hu. leucine zipper-EF-hand containing transmembraneprotein 1 (LETM1)
431	PNCM-298	77499	Hu. ribosome binding protein 1, ES/130
432	PNCM-300	77500	Prosaposin
433	PNCM-310	77160	Hu. uveal autoantigen
434	PNCM-311	77504	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
435	PNCM-314	77506	Prosaposin
436	PNCM-316	77507	Hu. Protein Protein A kinase (PRKA) anchor protein (gravin) 12
437	PNCM-318	77508	Prosaposin
438	PNCM-320	77509	Hu. ribosome binding protein 1, ES/130
439	PNCM-321	77162	Hu.uveal autoantigen
440	PNCM-322	77163	Hu.chromodomain helicase DNA binding protein 1-like(CHD1L)
441	PNCM-324	77165	Hu.accessory proteins BAP31/BAP29,6C6-Ag,CDM
442	PNCM-326	77167	Hu.eukaryotic translation initiation factor 2, subunit 2(beta, 38kD) (EIF2S2)
443	PNCM-329	77169	Hu.uveal autoantigen
444	PNCM-331	77171	Hu. Prosaposin
445	PNCM-332	77172	Hu.alanyl (membrane) aminopeptidase (aminopeptidase N)
446	PNCM-333	77173	Hu. Prosaposin
447	PNCM-337	77175	Hu.,Similar to glucose regulated protein, 58kDa, cloneMGC:3178
448	PNCM-338	77176	Hu. M-phase phosphoprotein 1
449	PNCM-341	77178	Hu. cDNA DKFZp586F1918
450	PNCM-345	77180	Hu.accessory proteins BAP31/BAP29,6C6-

SEQ ID NO: (Full-Length cDNA)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
			Ag,CDM
451	PNCM-348	77510	Prosaposin

TABLE 5

Pancreas Tumor Sequences Showing no Signficant Similarity to Sequences in Genbank

SEQ ID NO: (Full-Length cDNA/Pro)	CLONE NAME	CLONE ID	GENBANK IDENTITY/SEQUENCE FROM BLASTN OF SEQID
184	PNCM-1	71231	
187	PNCM-4	71234	No match to bp376 – 50bp@92% w/prosaposin – 100bp no matchl
212	PNCM-30	71251	
213	PNCM-31	71252	
334, 335	PNCM-146	73444	

EXAMPLE 4

FULL-LENGTH SEQUENCE AND EXPRESSION ANALYSIS OF THE PN80E PANCREATIC TUMOR PROTEIN CDNA

The full-length sequence of the cDNA clone 80186, (partial sequence disclosed in SEQ ID NO:105), was determined and is disclosed in SEQ ID NO:454. This sequence was used to search against public databases and the results are described in Table 6.

Table 6

Database Search Results for clone 80186, pancreatic tumor candidate Pn80E

SEQ ID NO (Partial/Full-length):	Clone ID	Candidate Name	GenBank Blastn Results
105/454	80186	Pn80E	89% Mus musculus 18 days embryo cDNA, RIKEN full-length enriched library, clone:1110014B07-a secreted protein, with a C1q domain

The mRNA expression profile was then further analyzed by real-time PCR. The first-strand cDNA used in the quantitative real-time PCR was synthesized from 20 μg of total RNA that was treated with DNase I (Amplification Grade, Gibco BRL Life Technology, Gaithersburg, MD), using Superscript Reverse Transcriptase (RT) (Gibco BRL Life Technology, Gaithersburg, MD). Real-time PCR was performed with a GeneAmpTM 5700 sequence detection system (PE Biosystems, Foster City, CA). The 5700 system uses SYBR™ green, a fluorescent dye that only intercalates into double stranded DNA, and a set of gene-specific forward and reverse primers. The increase in fluorescence was monitored during the whole amplification process. The optimal concentration of primers was determined using a checkerboard approach and a pool of cDNAs from breast tumors was used in this process. The PCR reaction was performed in 25 μl volumes that included 2.5 μl of SYBR™ green buffer, 2 μl of cDNA template and 2.5 μl each of the forward and reverse primers for the gene of interest. The cDNAs used for RT reactions were diluted 1:10 for each gene of interest and 1:100 for the β-actin control. In order to quantitate the amount of specific cDNA (and hence initial mRNA) in the sample, a standard curve was generated for each run using the plasmid DNA containing the gene of interest. Standard curves were generated using the Ct values determined in the real-time PCR which were related to the initial cDNA concentration used in the assay. Standard dilution ranging from 20-2 x 10^6 copies of the gene of interest was used for this purpose. In addition, a standard curve was generated for β-actin ranging from 200 fg-2000 fg. This enabled standardization

of the initial RNA content of a tissue sample to the amount of β-actin for comparison purposes. The mean copy number for each group of tissues tested was normalized to a constant amount of β-actin, allowing the evaluation of the over-expression levels seen with each of the genes.

Real-time PCR analysis as described above showed that Pn80E is over-expressed in a panel of pancreatic tumors, including metastatic tumors. Pn80E is also expressed in normal pancreas tissue, adrenal gland, aorta, skin and trachea. Low levels of expression were observed in bone, brain, bronchus, colon, esophagus, heart, kidney, liver, lung, pituitary, skeletal muscle, spinal cord, and spleen. These differential expression patterns indicate that this antigen may be used for immunotherapeutic purposes and/or as a diagnostic marker in individuals with pancreatic cancer.

EXAMPLE 5

FULL-LENGTH SEQUENCE AND EXPRESSION ANALYSIS OF THE PN81E PANCREATIC TUMOR PROTEIN CDNA

The full-length sequence of the cDNA clone 80207, (partial sequence disclosed in SEQ ID NO:128), was determined and is disclosed in SEQ ID NO:455. No matches were identified when this sequence was used to search agains public databases.

The mRNA expression profile of Pn81E was then analyzed by real-time PCR as described in Example 4. This analysis showed that Pn81E is over-expressed in a panel of pancreatic tumors and normal pancreas samples as compared to a panel of normal tissues including bone marrow, esophagus, gall bladder, heart, kidney, lung, skeletal muscle, small intestine, and stomach. Expression was observed in bone, PBMC, and spleen. Lower levels of expression were observed in brain, bronchus, colon, liver, pituitary gland, skin, spinal chord, and trachea. These results indicate that the Pn81E antigen may be used in diagnostic and immunotherapy applications.

EXAMPLE 6

PREPARATION OF A PCR-BASED cDNA SUBTRACTION LIBRARY FROM PANCREATIC TUMORS

A cDNA subtraction library containing cDNA from primary pancreatic tumors subtracted with cDNA from normal tissues (liver, salivary gland, small intestine, stomach, heart, brain, bone marrow and normal lung) was constructed as follows. Total RNA was extracted from primary tissues using Trizol reagent (Gibco BRL Life Technologies, Gaithersburg, MD) as described by the manufacturer. The polyA+ RNA was purified using an oligo(dT) cellulose column according to standard protocols. First strand cDNA was synthesized using the primer supplied in a Clontech PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA). The driver DNA consisted of cDNAs from normal tissues with the tester cDNA being from two primary pancreatic tumors. Double-stranded cDNA was synthesized for both tester and driver, and digested with a combination of endonucleases (MluI, MscI, PvuII, SalI and StuI) which recognize six-nucleotide restriction sites. This modification of the digestion procedure resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. The digested tester cDNAs were ligated to two different adaptors and the subtraction was performed according to Clontech's protocol.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step

resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that r are transcripts that are overexpressed in pancreatic tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

The resulting PCR products were subcloned into the TA cloning vector, pCRII (Invitrogen, San Diego, CA) and transformed into ElectroMax *E. coli* DH10B cells (Gibco BRL Life, Technologies) by electroporation. DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division (Foster City, CA) Automated Sequencer Model 373A.

Seventy three randomly selected cDNA clones in the subtracted pancreatic tumor-specific cDNA library were characterized by DNA sequencing and by subsequent Genbank and EST Blast database searches. Sequences of these partial cDNAs are provided in SEQ ID NO:456-528.

Three thousand seven hundred forty four randomly selected cDNA clones in the subtracted pancreatic tumor-specific cDNA library were characterized by DNA sequencing and by subsequent Genbank and EST Blast database searches. Sequences of these partial cDNAs are provided in SEQ ID NO:529-4346.

EXAMPLE 7

MICROARRAY AND SEQUENCE ANALYSIS OF CDNA CLONES OVEREXPRESSED IN PANCREAS TUMORS

One hundred thirty-eight individual clones analyzed using microarray technology as described in Example 2 showed between 3 to 4.5-fold overexpression in pancreas tumors as compared to normal tissues. These cDNA clones were sequenced using standard protocols and compared to public databases (SEQ ID NO:4347-4484). Those cDNAs that showed some degree of similarity to sequences in the databases are described in Table 7. Those cDNAs showing no significant similarity to known sequences in the database are described in Table 8.

TABLE 7

Pancreas Tumor cDNA Clones Showing Some Degree of Similarity to Sequences in Genbank

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig	Genbank
4346	p0150r10c11	R0580 C6	4.18	0.341	0.082	61	1	Secretogranin II (Chromogranin C)
4347	p0150r07c17	R0579 E9	3.68	0.163	0.044	42	1	Secretogranin II (Chromogranin C)
4348	p0150r09c15	R0580 A8	3.63	0.236	0.065	53	1	Secretogranin II (Chromogranin C)
4349	p0150r07c14	R0579 F7	3.01	0.214	0.071	46	1	Secretogranin II (Chromogranin C)
4350	p0150r11c05	R0580 E3	4.38	0.096	0.022	66	1	Secretogranin II (Chromogranin C)
4351	p0160r06c18	R0619 D9	3.43	0.266	0.077	134	2	Pancreatic Lipase
4352	p0160r02c21	R0618 C11	3.6	0.202	0.056	133	2	Pancreatic Lipase
4353	p0160r13c02	R0621 B1	3.24	0.202	0.062	135	2	Pancreatic Lipase
4354	p0150r13c04	R0581 B2	3.66	0.188	0.051	84	3	Secretogranin II (Chromogranin C)
4355	p0150r02c15	R0578 C8	4.45	0.131	0.029	11	3	Secretogranin II (Chromogranin C)
4356	P0150r06c12	R0579 D6	3.02	0.274	0.091	39	4	ATP binding cassette, subfamily B (MDR 1)
4357	p0151r06c12	R0583 D6	3.4	0.112	0.033	104	5	Human gene for JKTBP2, JKTBP1
4358	P0150r14c04	R0581 D2	3.17	0.161	0.051	87	6	26S proteasome regulatory subunit
4359	p0150r02c06	R0578 D3	3.28	0.193	0.059	14	7	Chromosome 5 CTC-487M23
4360	p0150r04c19	R0578 G10	3.91	0.192	0.049	23	8	cDNA clone FLJ21238 fis, clone COL01115
4361	p0150r03c18	R0578 F9	3.94	0.163	0.041	22	9	GTP cyclohydrolase 1
4362	p0151r13c03	R0585 A2	3.51	0.249	0.071	108	10	Clone RP11-353C18 on chromosome 20
4363	p0150r01c08	R0578 B4	3.86	0.171	0.044	5	11	Spectrin SH3 domain binding protein 1
4364	p0150r11c07	R0580 E4	3.02	0.143	0.048	67	12	Human decay accelerating factor (CD55) gene
4365	P0150r02c11	R0578 C6	3.33	0.148	0.045	10	13	BAC clone GS1-66B6 7p15.2-p13
4366	p0150r01c17	R0578 A9	4.14	0.202	0.049	2	14	RNA (guanine-7-) methyltransferase
4367	p0150r05c16	R0579 B8	3.63	0.131	0.036	32	15	Clone RP1-154G14 on chromosome 6q15-16.3

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig	Genbank
4368	p0150r06c04	R0579 D2	3.82	0.315	0.083	36	16	Human sarcomeric muscle protein
4369	p0150r15c17	R0581 E9	3.18	0.104	0.033	92	17	Clone 20I3 on chromosome Xq25-26
4370	p0150r15c11	R0581 E6	3.47	0.147	0.043	91	18	Human cytoplasmic dynein intermediate chain isoform IC-2
4371	p0150r09c13	R0580 A7	3.9	0.143	0.037	52	19	Human aldehyde dehydrogenase 1
4372	p0150r13c03	R0581 A2	3.14	0.222	0.071	80	20	cDNA DKFZp434C2112
4373	p0150r09c10	R0580 B5	3.03	0.226	0.075	57	21	Human RAD21 homolog
4374	p0161r13c17	R0625 A9	3.39	0.217	0.064	136	22	Pancreatic carboxypeptidase B1
4375	p0159r16c21	R0617 G11	4.1	0.2	0.049	132	23	Human matix metalloproteinase 2
4377	p0151r09c19	R0584 A10	3.31	0.139	0.042	106	25	Clone RP1-315G1 on chromosome Xq24-25
4378	p0151r02c06	R0582 D3	3.46	0.326	0.094	101	26	cDNA FLJ20882 fis, clone ADKA03206
4379	p0150r16c06	R0581 H3	3.37	0.155	0.046	100	27	Human potassium channel modulatory factor
4380	p0150r09c12	R0580 B6	4	0.111	0.028	58	28	Human proprotein convertase subtilisin/kexin type 2
4381	p0150r07c06	R0579 F3	3.37	0.195	0.058	43	29	KIAA0205 gene
4382	p0150r06c19	R0579 C10	3.34	0.178	0.053	34	30	Human thymidylate synthase
4383	p0150r04c05	R0578 G3	3.72	0.218	0.059	24	31	Clone RP11-179B15
4384	p0150r03c21	R0578 E11	4.17	0.2	0.048	18	32	KIAA0970 protein
4385	p0150r15c07	R0581 E4	3.83	0.102	0.027	90	33	Human myosin X
4386	p0150r02c18	R0578 D9	4.48	0.143	0.032	16	33	Human myosin X
4387	p0150r10c15	R0580 C8	4.46	0.247	0.056	62	34	KIAA1360 protein
4388	p0150r07c05	R0579 E3	3.12	0.135	0.043	40	35	cDNA DKFZp586E2023
4389	p0150r06c08	R0579 D4	3.85	0.177	0.046	37	36	Human hypothetical protein FLJ10134
4390	p0150r01c24	R0578 B12	3.74	0.18	0.048	4	37	Human ALEX1 protein
4391	p0150r07c15	R0579 E8	3.13	0.272	0.087	41	38	Human tropomodulin
4392	p0150r02c23	R0578 C12	4.34	0.163	0.037	8	39	Human Kreisler maf-related leucine zipper homolog
4393	p0151r09c08	R0584 B4	4.44	0.393	0.089	107	40	Human histone acetyltransferase
4394	p0150r16c09	R0581 G5	3.55	0.238	0.067	95	41	Human coronin, actin-binding protein 1C
4395	p0150r14c11	R0581 C6	3.99	0.096	0.024	86	42	cDNA DKFZp761G2423
4396	p0151r05c12	R0583 B6	3.49	0.221	0.063	103	43	Human X-prolyl aminopeptidase-like

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig	Genbank
4397	p0150r12c23	R0580 G12	4.06	0.14	0.034	75	44	Clone RP4-758N20 on chromosome 1p31.3-32
4398	p0150r16c02	R0581 H1	3.09	0.093	0.03	98	45	KIAA1228 protein
4399	p0155r10c08	R0600 D4	3.07	0.245	0.08	121	46	cDNA DKFZp586I1419
4400	p0150r02c05	R0578 C3	3.82	0.174	0.046	9	47	Human uncharacterized hypothalamus protein HARP11
4401	p0150r09c04	R0580 B2	3.09	0.197	0.064	55	48	Human aldehyde dehydrogenase 1
4402	p0150r03c22	R0578 F11	3.45	0.133	0.039	21	49	Human secretory granule, neuroendocrine protein 1
4403	p0150r15c10	R0581 F5	3.1	0.111	0.036	94	50	Human I-beta-1,3-N-acetylglucosaminyltransferase
4404	p0150r13c20	R0581 B10	3.94	0.111	0.028	82	51	Human 12p13.3 BAC RPCI11-350L7
4405	p0150r08c18	R0579 H9	3.35	0.173	0.052	49	52	Human tumor differentially expressed 1
4406	p0150r09c22	R0580 B11	3.39	0.195	0.057	54	53	Human deoxycytidine kinase
4408	p0163r04c09	R0630 G5	3	0.283	0.094	138	55	Human hypothetical protein FLJ10540
4409	p0155r01c04	R0598 B2	4.2	0.377	0.09	116	56	Human collagen, type III, alpha 1
4410	p0152r16c22	R0589 H11	3.74	0.363	0.097	113	57	Human transmembrane 4 superfamily member 4 (TM4SF4)
4411	p0152r16c12	R0589 H6	3.09	0.292	0.095	114	58	Human chloride intracellular channel 1
4413	p0150r05c23	R0579 A12	4.1	0.189	0.046	27	60	Human N33 protein form 2
4414	p0150r11c09	R0580 E5	3.16	0.191	0.06	68	61	Human hypothetical protein (FLJ11127)
4415	p0150r13c22	R0581 B11	3.1	0.12	0.039	83	62	DNA sequence from clone 422G23 on chromosome 6q24
4416	p0150r11c17	R0580 E9	3.66	0.244	0.067	70	63	cDNA FLJ20935 fis, clone ADSE01534
4417	p0159r16c01	R0617 G1	4.4	0.183	0.042	131	64	Human carboxypeptidase A2
4418	p0156r16c21	R0605 G11	3.37	0.206	0.061	122	65	Human guanine nucleotide exchange factor
4419	p0150r06c15	R0579 C8	3.21	0.168	0.052	35	66	Human chromosome 5 clone CTC-315O24
4422	p0150r11c22	R0580 F11	4.29	0.17	0.04	72	69	Human RNA helicase II/Gu protein gene
4425	p0150r11c02	R0580 F1	3.65	0.207	0.057	71	72	Human carboxypeptidase E
4426	p0157r07c21	R0607 E11	3.88	0.192	0.049	126	73	Human cutaneous T-cell lymphoma tumor antigen se70-2
4427	p0150r16c17	R0581 G9	3.28	0.101	0.031	97	74	KIAA0393 protein

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig	Genbank
4428	p0155r03c08	R0598 F4	3.25	0.305	0.094	117	75	Human laminin, gamma 2
4429	p0150r07c10	R0579 F5	3.27	0.223	0.068	44	76	Human chromosome 5 clone CTC-576H9
4430	p0150r16c13	R0581 G7	3.58	0.166	0.046	96	77	Clone RP11-71J12 on chromosome 13
4431	p0150r06c10	R0579 D5	3.05	0.243	0.08	38	78	Human 3q26.2-27 BAC RPCI11-469J4
4432	p0150r02c16	R0578 D8	4.47	0.11	0.025	15	79	Human potassium inwardly-rectifying channel, subfamily J
4433	p0150r09c06	R0580 B3	4.25	0.176	0.042	56	80	KIAA1699 protein
4434	p0150r11c16	R0580 F8	3.49	0.178	0.051	74	81	Human somatostatin receptor 2
4435	p0150r01c13	R0578 A7	4.49	0.411	0.092	1	82	Humna claudin-12
4436	p0150r08c10	R0579 H5	3.29	0.238	0.073	48	83	Human tumor rejection antigen (gp96) 1
4438	p0159r14c18	R0617 D9	3.07	0.101	0.033	130	85	Human carboxypeptidase A2
4439	p0150r16c22	R0581 H11	3.09	0.304	0.098	99	86	Human cDNA FLJ12280 fis clone MAMMA1001744
4440	p0152r10c20	R0588 D10	4.4	0.157	0.036	110	87	Human guanine nucleotide-binding protein alpha-subunit
4441	p0150r13c23	R0581 A12	3.48	0.248	0.071	79	88	Human nuclear factor kappa-B DNA binding subunit
4442	p0150r12c10	R0580 H5	3.7	0.158	0.043	78	89	Human CD164 isoform delta 4
4443	p0150r09c18	R0580 B9	3.67	0.214	0.058	59	90	Human galectin-8 gene
4444	p0158r09c04	R0612 B2	4.14	0.14	0.034	129	91	Human cathepsin C
4445	p0150r08c09	R0579 G5	3.69	0.226	0.061	47	92	Human imidazoline receptor candidate
4446	p0150r11c11	R0580 E6	4.15	0.237	0.057	69	93	Human glutaminase isoform C
4447	p0150r15c01	R0581 E1	4.12	0.099	0.024	88	94	Human chromosome 5 clone CTD-2314G24
4448	p0157r07c01	R0607 E1	3.67	0.254	0.069	125	95	DNA from chromosome 19, cosmid F21856
4449	p0150r09c21	R0580 A11	3.49	0.169	0.048	51	96	Human false p73 target protein gene
4450	p0150r12c02	R0580 H1	3.31	0.173	0.052	76	97	cDNA FLJ12946 fis, clone NT2RP2005254
4451	p0150r03c17	R0578 E9	4.16	0.212	0.051	20	98	cDNA DKFZp434L1715
4453	p0150r05c20	R0579 B10	3.43	0.147	0.043	29	100	Human large conductance calcium-activated potassium channel beta
4454	p0150r05c04	R0579 B2	3.01	0.1	0.033	31	101	Human prostate tumor over expressed gene 1
4455	p0150r07c12	R0579 F6	3.59	0.191	0.053	45	102	Human alpha-L-fucosidase gene

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig	Genbank
4456	p0150r05c02	R0579 B1	3.15	0.205	0.065	28	103	Human N-terminal acetyltransferase complex ard1 subunit
4457	p0152r13c24	R0589 B12	3.44	0.207	0.06	111	104	Chromosome 19, cosmid F23669
4458	p0150r03c11	R0578 E6	3.05	0.159	0.052	19	105	Human IK cytokine, down-regulator of HLA II
4459	p0162r13c11	R0629 A6	3.07	0.133	0.043	137	106	Human thrombospondin 2
4460	p0151r13c15	R0585 A8	3.71	0.171	0.046	109	107	cDNA FLJ23160 fis, clone LNG09682
4461	p0150r03c01	R0578 E1	4.03	0.145	0.036	17	108	Human Na+/glucose cotransporter gene
4462	p0151r08c17	R0583 G9	3.57	0.131	0.037	105	109	Human death-associated protein
4463	p0150r01c02	R0578 B1	3.1	0.287	0.093	3	110	Human guanine nucleotide binding protein
4464	p0150r04c06	R0578 H3	3.93	0.158	0.04	25	111	Clone RP4-813B7 on chromosome 1
4465	p0150r09c19	R0580 A10	3.86	0.197	0.051	50	112	Human mitochondrion
4466	p0153r06c10	R0591 D5	3.78	0.294	0.078	115	113	Human DEAD/H box polypeptide 5
4467	p0150r02c20	R0578 D10	3.82	0.198	0.052	13	114	KIAA1317 protein
4468	p0155r09c08	R0600 B4	4.13	0.393	0.095	118	115	KIAA0883 protein
4471	p0150r13c02	R0581 B1	3.13	0.163	0.052	81	117	RNA binding motif protein 5
4473	p0150r11c23	R0580 E12	3.57	0.237	0.067	65	119	Human GTP cyclohydrolase 1
4474	p0155r10c24	R0600 D12	3.55	0.205	0.058	120	120	Human mitochondrial DNA control region
4475	p0157r06c03	R0607 C2	4.14	0.172	0.042	124	121	Ras-related C3 botulinum toxin substrate 1
4476	p0150r05c24	R0579 B12	3.83	0.157	0.041	30	122	Human hypothetical protein FLJ20391
4479	p0155r10c19	R0600 C10	3.73	0.274	0.073	119	125	KIAA0292 protein
4480	p0150r14c23	R0581 C12	3.51	0.14	0.04	85	126	ISL1 transcription factor, LIM/homeodomain
4481	p0150r10c19	R0580 C10	3.56	0.188	0.053	60	127	KIAA0766 gene
4482	p0150r11c19	R0580 E10	3.28	0.152	0.046	63	128	KIAA1554 protein
4483	p0150r15c21	R0581 E11	3.25	0.114	0.035	89	129	Chromosome 11p14.3 PAC clone pDJ239b22
4484	p0150r11c21	R0580 E11	3.07	0.165	0.054	64	130	Clone RP1-309F20 on chromosome 20
4412	p0150r01c16	R0578 B8	3.06	0.242	0.079	7	59	Human thyroid hormone receptor coactivating protein

TABLE 8

Pancreas Tumor cDNAs Showing no Significant Similarity to Known Sequences in Genbank

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Genset	Contig
4376	p0150r02c02	R0578 D1	3.62	0.193	0.053	12	24
4407	p0157r08c09	R0607 G5	3.18	0.155	0.049	128	54
4420	p0151r05c04	R0583 B2	3.01	0.145	0.048	102	67
4421	p0150r05c21	R0579 A11	3.4	0.217	0.064	26	68
4423	p0150r01c14	R0578 B7	3.67	0.19	0.052	6	70
4424	p0150r15c08	R0581 F4	3.06	0.111	0.036	93	71
4437	p0150r05c18	R0579 B9	3.98	0.164	0.041	33	84
4452	p0157r07c20	R0607 F10	3.09	0.158	0.051	127	99
4469	p0152r16c01	R0589 G1	3.13	0.242	0.077	112	116
4471	p0150r12c22	R0580 H11	4	0.15	0.037	77	118
4476	p0150r11c04	R0580 F2	4.03	0.175	0.043	73	123
4477	p0156r16c18	R0605 H9	3.03	0.201	0.066	123	124

EXAMPLE 8

MICROARRAY AND SEQUENCE ANALYSIS OF ADDITIONAL CDNA CLONES OVEREXPRESSED IN PANCREAS TUMORS

Forty eight hundred clones from three PCR-based subtracted cDNA libraries were PCR amplified and arrayed on DNA chips. They were hybridized with fluorescently labeled probes which were generated from pancreatic tumors and a varity of normal tissues including normal pancreas. The array data were analyzed by computer and by visual analysis. Sixty-three clones with 4.5-fold overexpression in pancreatic tumors were selected and their sequences were determined by DNA sequencing (SEQ ID NO:4485-4547). The sequences were then searched against public databases including Genbank and EST. Those cDNAs that showed some degree of similarity to sequences in the databases are described in Table 9. Those cDNAs showing no significant similarity to known sequences in the database are described in Table 10. Several of these cDNAs have been

selected as promising candidates for therapeutic and diagnostic purposes. The candidate names are also shown in Tables 9 and 10.

TABLE 9

Additional Pancreas Tumor cDNA Clones Showing Some Degree of Similarity to Sequences in the Genbank

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Contig	Identity	Candidate
4533	p0157r07c23	R0607 E12	15.8	0.097	0.006	46	BAC clone CTA-271G13 from 7	
4518	p0157r05c17	R0607 A9	16.36	0.169	0.01	31	cDNA FLJ12849 fis, clone NT2RP2003393	
4506	p0150r09c01	R0580 A1	9.73	0.106	0.011	19	cDNA FLJ21368 fis, clone COL03056 Glutaminase isoform C	
4519	p0157r07c13	R0607 E7	46.35	0.12	0.003	32	cDNA FLJ21410 fis, clone COL03938	
4521	p0157r07c15	R0607 E8	12.34	0.137	0.011	34	cDNA FLJ23607 fis, clone LNG16050	Pn1474P
4507	p0150r08c17	R0579 G9	5.2	0.137	0.026	20	Chromogranin B	Pn1468P
4514	p0150r12c08	R0580 H4	7.88	0.046	0.006	27	Chromosome 12 clone 917O5	
4524	p0152r06c10	R0587 D5	11.83	0.038	0.003	37	Chromosome 5 clone CTC-534A2	
4509	p0150r09c20	R0580 B10	6.1	0.131	0.021	22	Chromosome 5 clone CTD-2031P19	
4500	p0150r11c01	R0580 E1	6.34	0.14	0.022	13	Chromosome 5 clone CTD-2122K7	Pn1469P
4523	p0155r07c16	R0599 F8	4.7	0.107	0.023	36	Chromosome 7 clone RP11-248K17 Caldesmon, 3' UTR	
4487	p0157r07c17	R0607 E9	8.97	0.148	0.017	4	Clone 27K12 on chromosome 6p11.2-12.3	
4539	p0157r07c09	R0607 E5	5.64	0.262	0.046		Clone RP1-122P22 on chromosome 20	Pn1473P
4501	p0150r03c14	R0578 F7	9.86	0.138	0.014	14	Clone RP11-239L20 on chromosome 6	
4529	p0157r05c18	R0607 B9	24.3	0.174	0.007	42	Discoidin domain receptor family. Human mammary carcinoma kinase	Pn1472P
4498	p0150r02c07	R0578 C4	4.99	0.264	0.053	11	DKFZp434M1616	
4508	p0150r09c17	R0580 A9	16.97	0.121	0.007	21	Guanine nucleotide binding protein (neuroendocrine secretory protein 55)	
4510	p0150r08c06	R0579 H3	5.32	0.113	0.021	23	Hormone-regulated Repro-PC 1.0 gene Reprogen Inc. KIAA1342	
4537	p0151r12c17	R0584 G9	5.37	0.937	0.174		Human breast tumor protein immunogenic fragment	

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Contig	Identity	Candidate
4513	p0150r11c03	R0580 E2	19.29	0.096	0.005	26	Human CGI-86 protein	
4546	p0157r07c06	R0607 F3	16.6	0.18	0.011		Human clone PP722 unknown mRNA	
4540	p0157r08c05	R0607 G3	20.8	0.353	0.017		Human colon cancer nucleotide sequence, NCA	Pn1475P
4526	p0150r02c03	R0578 C2	5.65	0.166	0.029	39	Human decidual protein induced by progesterone	
4517	p0150r15c23	R0581 E12	7.72	0.143	0.019	30	Human desmoplakin	
4530	p0157r06c17	R0607 C9	8.13	0.222	0.027	43	Human filamin gene (FLNB)	
4504	p0150r01c04	R0578 B2	10.45	0.095	0.009	17	Human foetal brain secreted protein	
4534	p0150r01c20	R0578 B10	4.82	0.295	0.061		Human Hexosaminidase B beta-subunit	
4496	p0150r07c01	R0579 E1	8.7	0.107	0.012	9	Human HLA gene for MHC class I antigen, B4701 allele MDM2 gene	
4484	p0157r05c22	R0607 B11	8.32	0.211	0.025	1	Human long-chain fatty acid coenzyme A ligase 5	
4488	p0150r15c22	R0581 F11	9.35	0.115	0.012	5	Human putative helicase RUVBL (LOC56897)	
4511	p0150r13c19	R0581 A10	5.09	0.217	0.043	24	Human PVR gene	
4503	p0150r04c17	R0578 G9	6.29	0.404	0.064	16	Human secreted protein gene 79	Pn1467P
4582	p0150r11c14	R0580 F7	31.67	0.1	0.003	41	Human secretory granule, neuroendocrine protein 1	
4485	p0157r05c21	R0607 A11	5.18	0.149	0.029	2	Human sucrase-isomaltase	
4531	p0157r07c18	R0607 F9	38.09	0.183	0.005	44	Human transgelin	
4544	p0162r02c05	R0626 C3	5.16	0.434	0.084		hXAG	
4486	p0157r06c05	R0607 C3	9.62	0.128	0.013	3	KIAA0071	
4527	p0150r06c24	R0579 D12	4.75	0.112	0.024	40	KIAA0804	
4516	p0150r09c11	R0580 A6	5.32	0.227	0.043	29	KIAA1289	
4541	p0157r08c17	R0607 G9	5.59	0.213	0.038		Malate dehydrogenase 2, NAD	
4495	p0150r05c19	R0579 A10	11.78	0.112	0.01	9	MDM2 gene	
4536	p0150r15c06	R0581 F3	6.86	0.227	0.033		Neuroendocrine secretory protein 55	
4489	p0159r03c13	R0614 E7	5.97	0.549	0.092	6	Pancreatic lipase	
4490	p0160r04c18	R0618 H9	4.68	0.374	0.08	6	Pancreatic lipase	
4545	p0157r06c24	R0607 D12	18.84	0.157	0.008		Pro alpha 1(I) collagen	
4515	p0150r05c22	R0579 B11	4.63	0.187	0.04	28	PRO2000 protein	

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Contig	Identity	Candidate
4520	p0157r07c14	R0607 F7	26.74	0.149	0.006	33	Protein identified by the signal sequence trap polyA site DNA	
4543	p0161r16c06	R0625 H3	5.96	1.13	0.19		Regenerating islet-derived 1 beta	
4491	p0150r06c23	R0579 C12	4.79	0.133	0.028	7	RP11-287F15 chromosome 9	
4492	p0150r02c15	R0578 C8	4.45	0.131	0.029	7	RP11-287F15 chromosome 9	
4493	p0150r13c24	R0581 B12	6.41	0.138	0.021	8	Secretogranin II	
4494	p0150r15c03	R0581 E2	6.13	0.129	0.021	8	Secretogranin II	
4502	p0150r02c12	R0578 D6	6.07	0.149	0.025	15	Secretogranin II	
4505	p0150r02c22	R0578 D11	5.65	0.147	0.026	18	Secretogranin II	

TABLE 10

Additional Pancreas Tumor cDNAs Showing no Significant Similarity to Known Sequences in Genbank

SEQ ID NO:	Element (384)	Element (96)	Ratio	Median Signal 1	Median Signal 2	Contig	Candidate
4497	p0150r06c16	R0579 D8	4.93	0.105	0.021	10	
4499	p0152r15c23	R0589 E12	4.91	0.186	0.038	12	Pn1471P
4512	p0150r12c09	R0580 G5	4.6	0.083	0.018	25	
4522	p0151r01c08	R0582 B4	5.1	0.158	0.031	35	
4525	p0150r04c18	R0578 H9	5.3	0.145	0.027	38	
4532	p0157r06c08	R0607 D4	11.23	0.093	0.008	45	
4535	p0150r14c15	R0581 C8	5.19	0.102	0.02		Pn1470P
4538	p0155r12c15	R0600 G8	5.35	0.772	0.145		
4542	p0160r03c01	R0618 E1	4.73	0.489	0.104		Pn1476P

EXAMPLE 9

QUANTITATIVE REAL-TIME PCR ANALYSIS OF cDNA CLONES OVEREXPRESSED IN PANCREATIC TUMORS

Four pancreas clones selected by cDNA microarray and subtracted cDNA library as described in Examples 2 and 6-8 were analyzed by real-time PCR to confirm their expression level in a varity of tissues. Pancreatic tumors and normal pancreas tissues along with other normal tissues were tested in quantitative real-time PCR. Briefly, the first-strand cDNA was synthesized from 20μg of total RNA that had been treated with DNase I (Amplification Grade, Gibco BRL Life Technology, Gaitherburg, MD), using Superscript Reverse Transcriptase (RT) (Gibco BRL Life Technology, Gaitherburg, MD). Real-time PCR was performed with a GeneAmp™ 5700 sequence detection system (PE Biosystems, Foster City, CA). The 5700 system uses SYBR™ green, a fluorescent dye that only intercalates into double stranded DNA, and a set of gene-specific forward and reverse

primers. The increase in fluorescence is monitored during the whole amplification process. The optimal concentration of primers was determined using a checkerboard approach and a pool of cDNAs from pancreas tumors was used in this process. The PCR reaction was performed in 25μl volumes that include 2.5μl of SYBR green buffer, 2μl of cDNA template and 2.5μl each of the forward and reverse primers for the gene of interest. The cDNAs used for RT reactions were diluted 1:10 for each gene of interest and 1:100 for the β-actin control. In order to quantitate the amount of specific cDNA (and hence initial mRNA) in the sample, a standard curve is generated for each run using the plasmid DNA containing the gene of interest. Standard curves were generated using the Ct values determined in the real-time PCR which were related to the initial cDNA concentration used in the assay. Standard dilution ranging from 20-2x10^6 copies of the gene of interest was used for this purpose. In addition, a standard curve was generated for β-actin ranging from 200fg-2000fg. This enabled standardization of the initial RNA content of a tissue sample to the amount of β-actin for comparison purposes. The mean copy number for each group of tissues tested was normalized to a constant amount of β-actin, allowing the evaluation of the over-expression levels seen with each of the genes.

Pn1467P (SEQ ID NO:4503) was found to be over-expressed in grade IV pancreas tumors and the majority of grade III tumors. Moderate expression was observed in grade II tumors, normal pancreas, and in most normal tissues. Over-expression of Pn1470P (SEQ ID NO:4535) was seen in grade III tumors and normal pancreas. Moderate expression of this gene was observed in grade IV tumors. Over-expression was also seen in bronchus. Low to moderate expression was observed in gall bladder, PBMC, stomach testis, and thymus. Pn1475P (SEQ ID NO:4540) was over-expressed in grades II-IV pancreas tumors and expressed at a low level in normal pancreas. Expression was not seen in metastatic tumors or in pancreatitis. Some Pn1475P expression was observed in bronchus, colon, esophagus, gall bladder, lung, salivary gland, small intestine, stomach, and trachea. Pn1476 (SEQ ID NO:4542) was overexpressed in 4 of 11 grade III tumors, 1 grade II, and 1 grade IV tumor. It was also overexpressed in 3 of 4 normal pancreas samples. No expression of this gene was observed in any normal tissues. Thus, this

candidate will be valuable for both vaccine and diagnostic purposes. Pn1468P (SEQ ID NO:4507) was over-expressed in pancreas tumor metastases but not in other pancreas tumors. Over-expression was also observed in adrenal gland and pituitary, but was absent from all other normal tissues. Pn1473P (SEQ ID NO:4539) was highly over-expressed in pancreas tumor sample T795A. It was also over-expressed in 1 of 3 grade II pancreas tumor samples, 2 of 6 grade 4 tumor samples, and 7 of 11 grade III tumor samples. It was also over-expressed in tumor metastases but was not expressed in normal pancreas tissue. Pn1473P expression was also observed in skeletal muscle, stomach, testis, and trachea. The expression profiles of all of these candidate genes suggest that they will be valuable for therapeutic vaccine and/or diagnostic purposes.

EXAMPLE 10

FULL LENGTH CDNA AND PROTEIN SEQUENCE FOR 4 ANTIGENS OVEREXPRESSED IN PACREATIC TUMORS

The sequences for Pn1468P, Pn1472P, and Pn1475P (SEQ ID NOs:4507, 4529, 4540, respectively), shown to be overexpressed in pancreas tumor samples, were searched against Genbank and the full length sequences identified. The full length sequences from Genbank are set forth in SEQ ID NOs:4548, 4549, and 4550, respectively. The corresponding protein sequences are set forth in SEQ ID NOs:4552-4554. The sequence for Pn1467, also overexpressed in pancreas tumor samples, was searched against the Genseq database and the full length sequence identified. The full length cDNA sequence from Genseq is set forth in SEQ ID NO:4547 and the corresponding protein sequence is set forth in SEQ ID NO:4551.

EXAMPLE 11

FULL LENGTH CDNA AND PROTEIN SEQUENCE FOR 2 ANTIGENS OVEREXPRESSED IN PACREATIC TUMORS

Disclosed herein are the full-length DNA and protein sequences for the Pn1509P and Pn1510P antigens, both overexpressed in pancreatic tumors as compared to normal tissues.

A partial sequence for Pn1509P was shown to be overexpressed by 3.74 fold in pancreatic tumors as compared to normal tissues (see SEQ ID NO:4410, Table 2). The full-length DNA sequence for Pn1509P was identified by searching the 493 base pair fragment of Pn1509P set forth in SEQ ID NO:4410 against the Genbank database. The full-length extended DNA sequence for Pn1509P (identified in GenBank accession number NM 004617) is set forth in SEQ ID NO:4555 and the corresponding protein is set forth in SEQ ID NO:4558. Based on sequence analysis, Pn1509 is predicted to be a tetraspan protein (it has four predicted membrane spanning domains) and has two potential sites for N-linked glycosylation.

A partial sequence for Pn1510P was shown to be overexpressed by 3.03 fold in pancreatic tumors as compared to normal tissues (see SEQ ID NO:4477, Table 2). The partial Pn1510P sequence set forth in SEQ ID NO:4477 was used in a search of the GeneSeq DNA database and matched 5 GeneSeq DNA records: A26456, A37144, A26424, V84525, and T22133. When the 5 protein coding regions of these DNA sequences were aligned using the DNAStar Seqman program, it was found that record A37144 had an additional C at position 35. This resulted in a 243 amino acid ORF. In the absence of this C at position 35, the DNA sequence encodes a 278 amino acid ORF. Disclosed herein are the DNA sequences that encode for both the 243 amino acid ORF and the 278 amino acid ORF (SEQ ID NOs:4556 and 4557, respectively). Also disclosed herein are the protein sequences for the 243 (Pn1510P-243) and 278 (Pn1510P-278) amino acid ORFs (SEQ ID NOs:4559 and 4560, respectively). In addition, transmembrane prediction programs were run to determine whether or not the Pn1510 protein may contain a transmembrane domain. Analysis of the Pn1510P-278 and Pn1510P-243 amino acid sequences using the PSORT

and PSORTII programs revealed no potential transmembrane domains. However, analysis of these 2 protein sequences using a transmembrane prediction program identified a stretch of 20 hydrophobic amino acids, suggesting a possible transmembrane domain. This transmembrane domain occurs at amino acids 233-252 of the Pn1510P-278 ORF and at amino acids 198-217 of the Pn1510P-243 ORF.

EXAMPLE 12

SYNTHESIS OF PEPTIDES

Polypeptides are synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence is attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support is carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides are precipitated in cold methyl-t-butyl-ether. The peptide pellets are then dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) is used to elute the peptides. Following lyophilization of the pure fractions, the peptides are characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 13

PEPTIDE PRIMING OF T-HELPER LINES

Generation of $CD4^+$ T helper lines and identification of peptide epitopes derived from tumor-specific antigens that are capable of being recognized by $CD4^+$ T cells in the context of HLA class II molecules, is carried out as follows:

Fifteen-mer peptides overlapping by 10 amino acids, derived from a tumor-specific antigen, are generated using standard procedures. Dendritic cells (DC) are derived from

PBMC of a normal donor using GM-CSF and IL-4 by standard protocols. $CD4^+$ T cells are generated from the same donor as the DC using MACS beads (Miltenyi Biotec, Auburn, CA) and negative selection. DC are pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 μg/ml. Pulsed DC are washed and plated at 1×10^4 cells/well of 96-well V-bottom plates and purified $CD4^+$ T cells are added at 1×10^5/well. Cultures are supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37°C. Cultures are restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 U/ml IL-2. Following 4 *in vitro* stimulation cycles, resulting $CD4^+$ T cell lines (each line corresponding to one well) are tested for specific proliferation and cytokine production in response to the stimulating pools of peptide with an irrelevant pool of peptides used as a control.

EXAMPLE 14

GENERATION OF TUMOR-SPECIFIC CTL LINES USING IN VITRO WHOLE-GENE PRIMING

Using *in vitro* whole-gene priming with tumor antigen-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines are derived that specifically recognize autologous fibroblasts transduced with a specific tumor antigen, as determined by interferon-γ ELISPOT analysis. Specifically, dendritic cells (DC) are differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC are infected overnight with tumor antigen-recombinant vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μg/ml CD40 ligand. Virus is then inactivated by UV irradiation. CD8+ T cells are isolated using a magnetic bead system, and priming cultures are initiated using standard culture techniques. Cultures are restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with previously identified tumor antigens. Following four stimulation cycles,

CD8+ T cell lines are identified that specifically produce interferon-γ when stimulated with tumor antigen-transduced autologous fibroblasts. Using a panel of HLA-mismatched B-LCL lines transduced with a vector expressing a tumor antigen, and measuring interferon-γ production by the CTL lines in an ELISPOT assay, the HLA restriction of the CTL lines is determined.

EXAMPLE 15

GENERATION AND CHARACTERIZATION OF ANTI-TUMOR ANTIGEN MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies are raised against *E. coli* derived tumor antigen proteins as follows: Mice are immunized with Complete Freund's Adjuvant (CFA) containing 50 μg recombinant tumor protein, followed by a subsequent intraperitoneal boost with Incomplete Freund's Adjuvant (IFA) containing 10μg recombinant protein. Three days prior to removal of the spleens, the mice are immunized intravenously with approximately 50μg of soluble recombinant protein. The spleen of a mouse with a positive titer to the tumor antigen is removed, and a single-cell suspension made and used for fusion to SP2/O myeloma cells to generate B cell hybridomas. The supernatants from the hybrid clones are tested by ELISA for specificity to recombinant tumor protein, and epitope mapped using peptides that spanned the entire tumor protein sequence. The mAbs are also tested by flow cytometry for their ability to detect tumor protein on the the surface of cells stably transfected with the cDNA encoding the tumor protein.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.